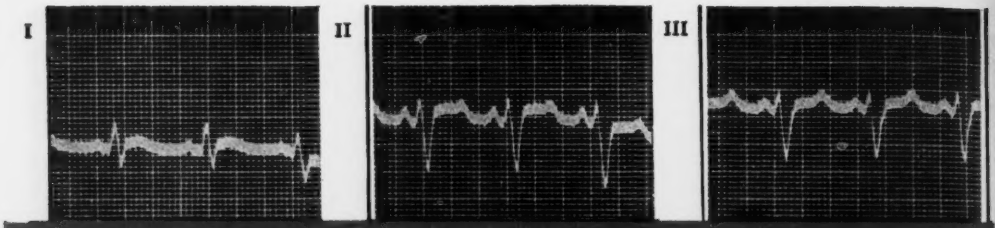
NOVEMBER 1955
VOL. XII NO. 5

Circulation

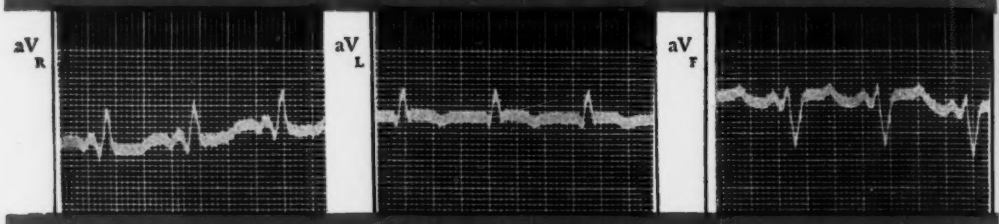
FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Published by Grune & Stratton, Inc.



REDUCE MORTALITY

in Myocardial Infarction with Severe Shock

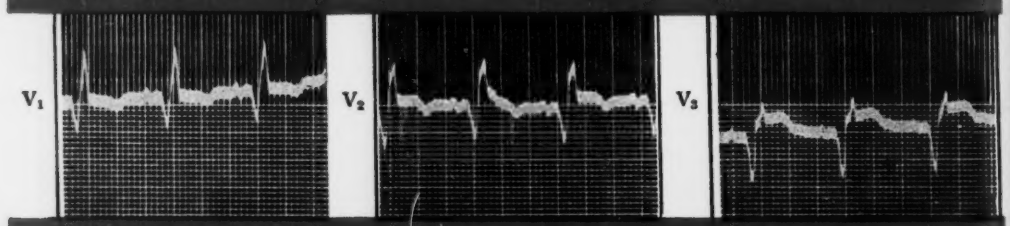


by the early use of

LEVOPHED®

BITARTRATE

the most powerful pressor antidote for shock



SUPPLIED:

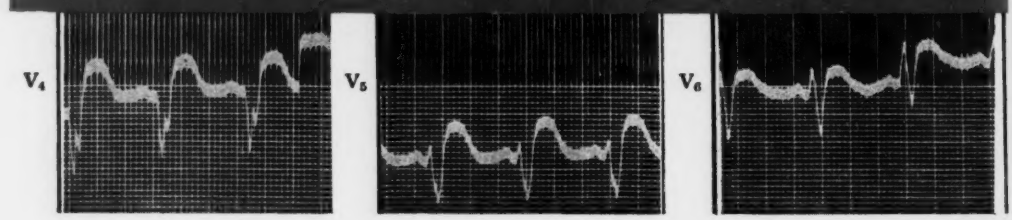
Levophed bitartrate 0.2% solution in ampuls of 4 cc., boxes of 10, to be administered in 1000 cc. of 5% dextrose solution in distilled water or 5% dextrose in saline solution.

Winthrop Stearns INC.

New York 18, N. Y. Windsor, Ont.

Write for detailed literature.

Levophed, trademark reg. U. S. Pat. Off., brand of levarterenol



Circulation

NOVEMBER 1955
VOL. XII NO. 5

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

The Influence of Rheumatic Fever on Serum Concentrations of the Enzyme, Glutamic Oxalacetic Transaminase

By IRWIN NYDICK, M.D., JAMES TANG, M.D., GENE H. STOLLERMAN, M.D., FELIX WRÓBLEWSKI, M.D. AND JOHN S. LADUE, M.D., PH.D.

Variations in serum concentration of the enzyme, glutamic oxalacetic transaminase, in 64 patients with rheumatic fever were studied. Elevations were noted in 17 of 26 patients with carditis of definite or questionable activity and transiently in one rheumatic subject with viral myocarditis. Except for one patient with polyarthritis and equivocal evidence of acute cardiac involvement, serum concentrations were normal during noncardiac rheumatic manifestations and inactive carditis. There was no relationship to temperature, sedimentation rate, white blood count or C-reactive protein. Intermittent necrosis of myocardial fibers probably leads to these increased serum transaminase concentrations.

THE enzyme, glutamic oxalacetic transaminase (GO-T), has been found in all human and animal sera that have been tested. This transaminase has been found in high concentration in heart muscle, skeletal muscle, brain, liver and kidney in decreasing order.[1, 2, 3] The concentration in lung is very low. Marked increases in serum concentrations of GO-T have been demonstrated during the acute phases of myocardial destruction of many types, including acute myocardial infarction in man,[4, 5] experimental myocardial infarction in dogs, either following coronary ligation[3] or the injection of plastic microspheres into the coronary circulation[7] and following the intravenous injection of papain into rabbits.[8, 9] The rises in serum glutamic oxalacetic transaminase (SGO-T) appear to be roughly proportional to the amount of myocardial necrosis. Striking elevations of the serum level follow acute or chronic liver damage[10, 11] and lesser rises occur after acute renal or skeletal muscle damage.[12, 3]

The serum level of glutamic oxalacetic transaminase has not been found to be elevated in a large group of patients with infectious, neoplastic, allergic and degenerative disease states unless evidence of acute damage to the liver, heart or skeletal muscle was present.

The observation that myocardial necrosis could be detected by measurement of the changes in the serum concentrations of glutamic oxalacetic transaminase led us to study alterations of enzyme concentration in different groups of rheumatic patients. Assay of the enzyme was performed by a simple rapid spectrophotometric method.[6] The results with this method are comparable with those of the more laborious chromatographic assay.[6]

Previously the acute phase reactants such as C-reactive protein (CRP)[13, 15] erythrocyte sedimentation rate, serum complement[14] and

From the Medical Service of the Memorial Center for Cancer and Allied Diseases, the Sloan-Kettering Division of Cornell University Medical College, the Department of Medicine of Cornell University Medical College and Irvington House and the Department of Medicine of New York University College of Medicine, New York, N. Y.

Supported in part by Grants H-1978 and H-903 (c) of the National Institute of Health and in part by funds of the New York Heart Association.

white blood cell count have been used as indices of rheumatic activity. It has been recognized that these are nonspecific tests of inflammation and that they do not measure, per se, involvement of the myocardial fiber. In this study, an attempt is made to observe the behavior of the serum transaminase in patients with rheumatic fever, with particular reference to those showing manifestations of carditis.

Material and Methods

The patients included in this study were admitted to Irvington House in the acute, chronic or convalescent stages of rheumatic fever or were seen as routine admissions to the wards of the Second (Cornell) Medical Division of Bellevue Hospital, The New York Hospital or the Memorial Center for Cancer and Allied Diseases. Blood for the serum transaminase determinations was obtained three times weekly from the Irvington House patients for periods ranging from two weeks to six months. The sera were coded and analyzed for transaminase activity. Patients from the other services were bled less frequently. Sera were frozen and then analyzed within one week.

The test for C-reactive protein was performed by the capillary precipitation method as described by Anderson and McCarty,[15] employing an antiserum prepared by injecting rabbits with purified, crystalline C-reactive protein of human origin. The erythrocyte sedimentation rate (ESR) was determined by the Wintrobe method and corrected for variations in hematocrit according to standard tables.

Liver function tests, performed in most patients exhibiting rises in serum levels of transaminase included sulfobromophthalein retention (BSP), serum alkaline phosphatase, cephalin flocculation and serum bilirubin determinations.

Measurement of Enzyme (SGO-T)

The spectrophotometric method of assay was used[6] (fig. 1), employing the Beckman (DU) spectrophotometer. In this method, the patient's serum is added to excesses of aspartic acid and α ketoglutaric acid buffered by one-tenth molar phosphate (pH 7.4) in the presence of reduced coenzyme I ($DPNH^+$) and an excess of malic dehydrogenase. The optical density of this solution decreases as reduced diphosphopyridine nucleotide ($DPNH^+$) is oxidized during the reaction. The rate of this reaction is limited only by the concentration of glutamic oxalacetic transaminase. One unit of transaminase is designated as a change in optical density of 0.001 per milliliter per minute at wavelength 340 μ. The normal range as determined in 150 healthy adults is 8 to 40 units per milliliter per minute (mean, 22.1; S.D., 7.1). The normal range in 75 healthy children was 10 to 40 units per milliliter per minute (mean, 25.1; S.D., 7.0). The standard deviation of any individual determination is approximately 5 per cent.

Diagnosis and Classification of Subjects

All of the patients included in this study met the criteria of Jones[16] for the diagnosis of rheumatic fever at some time during the course of their disease. Certain criteria were established in order to group the patients according to the probability of active cardiac involvement (table 1).

A child or adolescent was considered to show definitely active carditis if one or more of the following conditions was present: (1) congestive heart failure, (2) progressively enlarging heart, (3) pericarditis, as evidenced by a pericardial friction rub or a rapid enlargement of the cardiac silhouette on x-ray study compatible in size and form with that seen with pericardial effusions, (4) endocarditis, suggested by the appearance of a significant new murmur or definite increase in intensity of a pre-existing murmur and (5) the appearance of markedly abnormal T-waves on the electrocardiogram (prolongation of the P-R interval alone was not considered conclusive evidence of active carditis). Only one patient showed an abnormal electrocardiogram with no other evidence of myocarditis. This occurred during the course of virus pneumonia (table 1).

In the adult patients, in contrast to children, congestive heart failure, progressive cardiac enlargement or electrocardiographic abnormalities were not considered in themselves to be conclusive evidence of active carditis, unless gross or extensive microscopic evidence of activity was present in the heart at autopsy.

Group I includes only patients with rheumatic fever with active carditis. The presence of congestive heart failure formed the basis for a further division of this group, since the carditis responsible for the congestive failure in these patients was likely to be most severe.

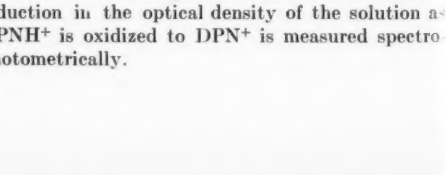


Fig. 1. The transamination reaction is shown. The reduction in the optical density of the solution as $DPNH^+$ is oxidized to DPN^+ is measured spectrophotometrically.

Group II includes patients with rheumatic fever and previously known rheumatic heart disease. The evidence for active cardiac involvement was considered to be equivocal in the absence of the appearance of new cardiac manifestations during the observed attack, despite laboratory evidence of continuing inflammation.

Group III contains two categories of patients with rheumatic fever, but with no known cardiac involvement; (1) polyarthritis, (2) chorea or erythema marginatum.

Group IV is composed of patients with inactive rheumatic fever but with known carditis in the past. This group is further divided into children convalescing from a recent attack of active carditis and adults who have recovered from rheumatic fever years previously and at present show inactive rheumatic heart disease.

The period of convalescence is dated from the day suppressive antirheumatic therapy was withdrawn if no laboratory or clinical evidence of an exacerbation of rheumatic activity supervened during the following two months.[18]

Group V contains patients with inactive rheumatic fever who developed virus pneumonia.

Group VI is composed of 16 patients with active rheumatoid arthritis (no evidence of cardiac involvement) and osteoarthritis..

The behavior of the transaminase in the untreated rheumatic could not be studied adequately because so many of the patients showed severe cardiac involvement and it was believed necessary to administer steroids or salicylates in an attempt to suppress inflammation.

Results

The 80 patients studied are listed in table 1. The incidence of abnormal serum levels of the enzyme can be seen in this table. Of nine patients who showed signs of active carditis with congestive heart failure (group I,a), the serum transaminase was abnormal at some time in eight. Of eight patients with active carditis who did not develop congestive heart failure (table 1, group I,b) only three showed any abnormality of the enzyme (SGO-T). Elevated serum levels of transaminase were seen in 6 of 9 patients with rheumatic fever and known cardiac disease but without definite clinical evidence of activity of the carditis (group II). The high incidence of abnormal results in this group may be due to the fact that five adults with suspected chronically smoldering carditis on the basis of persistent laboratory evidence of inflammation without frank clinical activity are included. One of these adults had congestive heart failure.

Table 1.—*Clinical Material: Incidence of Elevated Serum Glutamic Oxalacetic Transaminase (SGO-T)*

	Number of Patients	Number of Patients Abnormal	Number of Tests	Number of Tests Abnormal
I Active Rheumatic Carditis				
(a) With Congestive Failure	9	8	267	51
(b) Without Congestive Failure	8	3	231	14
II Questionably Active Rheumatic Carditis	9	6	64	13
III Rheumatic Fever without Cardiac Involvement				
(a) Polyarthritis	3	1	71	15
(b) Chorea and Erythema Marginatum	9	0	101	0
IV Inactive Rheumatic Fever —Previous Carditis				
(a) Recent—Convalescent	12	0	96	0
(b) Remote—Adults with RHD	6	0	32	0
V Virus Pneumonia in Rheumatic Subjects	8	1	31	1
VI Rheumatoid Arthritis—Active	16	0	35	0

The high incidence of elevations of serum glutamic oxalacetic transaminase is shown in patients with rheumatic carditis of definite or questionable activity. Note the two exceptions, one patient with polyarthritis and the other with virus pneumonia. (See text for discussion.)

Only 2 of the 54 patients in the other groups had abnormal serum glutamic oxalacetic transaminase levels at any time. These two patients showed suggestive evidence of cardiac involvement. One patient had virus pneumonia with T-wave inversions in the electrocardiogram, the other, acute rheumatic polyarthritis (case 5, J. B., see below). In all of the other patients, the transaminase concentration was consistently normal. The conditions studied included rheumatic fever manifested by polyarthritis, erythema marginatum or chorea minor without cardiac involvement, inactive rheumatic fever after previous carditis, virus pneumonia in rheumatic fever subjects and

active rheumatoid and osteoarthritis. Spinal fluid transaminase was normal in the three chorea patients studied and in four acute rheumatic fever patients without chorea. One of the latter patients showed normal (11 units) spinal fluid transaminase content when his serum concentration was elevated to 61 transaminase units.

Nine individuals were studied during and after reactions to intramuscularly administered benzathine penicillin. The reactions ranged in severity from local tenderness and induration of the muscles to a generalized urticaria with polyarthritis. The transaminase was normal on all occasions.

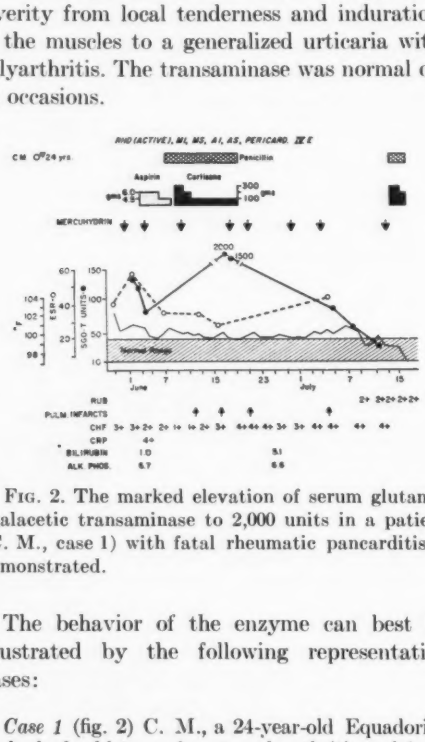


FIG. 2. The marked elevation of serum glutamic oxalacetic transaminase to 2,000 units in a patient (C. M., case 1) with fatal rheumatic pancarditis is demonstrated.

The behavior of the enzyme can best be illustrated by the following representative cases:

Case 1 (fig. 2) C. M., a 24-year-old Equadorian male, had a history of acute polyarthritis and fever five years prior to admission in March of 1949, which was treated at that time with aspirin for three months. No specific information is available concerning evidence of cardiac involvement at that time, but during the three years prior to his final hospitalization, he complained of progressively severe dyspnea, cough and intermittent scanty hemoptysis. Diffuse aching precordial pain had been present for six months. Three months prior to this admission, he developed anorexia, perspired freely, became more short of breath, lost 30 pounds of weight and required digitalis during this period.

Examination showed a dyspneic, perspiring patient with distended neck veins, a temperature of 102 F., blood pressure of 140/40, a heart rate of 120 per minute, and respirations of 24 per minute. A pleural friction rub was heard over the left chest and subcrepitant rales were heard over the lower halves of both lungs. The heart was enlarged beyond the midaxillary line. The murmurs of mitral stenosis and insufficiency and aortic stenosis and insufficiency were heard. A pericardial friction rub was first heard on the thirty-ninth hospital day. The liver edge was felt 3 cm. below the costal margin.

The patient showed moderate improvement until June 10 when a shock-like episode associated with chest pain and hemoptysis occurred. This was interpreted as due to pulmonary embolization. Despite the administration of heparin and Dicumarol, pulmonary embolization recurred on three separate occasions. After June 12 he became progressively more dyspneic and expired on July 16.

During June, a five-day course of aspirin was discontinued because of salicylate toxicity and cortisone was administered for a short period in amounts inadequate to suppress any of the laboratory signs of inflammation. A low-grade fever persisted, the sedimentation rate ranged from 30 to 60 mm. in 1 hour, and the white blood cell count never fell below 11.2 thousand.

The electrocardiogram was interpreted as showing biventricular hypertrophy. On admission the bilirubin was 1.0 mg. per 100 cc. and the alkaline phosphatase 6.7 Bodansky units. On June 24, following three pulmonary emboli, the bilirubin was 5.1 mg. per 100 cc. and the alkaline phosphatase unchanged. The blood urea nitrogen was normal on all occasions.

The serum glutamic oxalacetic transaminase showed striking alterations. It was 140 units on admission at a time when there was moderate heart failure, signs of mild liver dysfunction and before pulmonary emboli had occurred. Pulmonary emboli occurred on June 12 and 16. A rise of serum transaminase to 2,000 units (the highest recorded in this series) occurred on June 18. The bilirubin subsequently rose and heart failure became more severe. Despite intractable heart failure, another pulmonary embolus and the appearance of a pericardial friction rub, the serum transaminase level gradually fell to normal before the patient died.

At autopsy, the heart weighed 735 Gm., an extensive fibrinous pericarditis was seen, all chambers were dilated and their walls hypertrophied, and the mitral, aortic and tricuspid valves showed typical nonbacterial rheumatic involvement. Multiple small and moderate sized pulmonary infarcts were present. The liver and lungs were moderately congested.

Microscopic examination of the heart revealed extensive acute inflammation of the pericardium, myocardium and endocardium. Many Aschoff nodules and Antischkow myocytes were seen.

Deposition of fibrin, infiltration with polymorphonuclear leucocytes, lymphocytes and histiocytes, fibrinoid degeneration of collagen and extensive vascular granulation tissue were present. The myocardial fibers showed hypertrophy and there were multiple areas where they were vacuolated, necrotic and showed an increased amount of fat. There was congestion of the central veins of the liver with a small amount of necrosis in the surrounding cells.

Comment. This was a fatal case of extensive, acute, rheumatic pancarditis. There were striking elevations of the serum glutamic oxalacetic transaminase. The peak elevations of the enzyme did not coincide with the maximum severity of congestive heart failure or liver dysfunction. The relationship of pulmonary infarction to the maximum rise is not clear. Transaminase was elevated initially before clinical signs of pulmonary infarction appeared. It is of interest that the level of transaminase fell to normal when the patient was critically ill, a few days before death, although extensive microscopic evidence of acute rheumatic fever was found at autopsy.

Liver cell injury undoubtedly contributed to the elevations of the serum glutamic oxalacetic transaminase but liver cell necrosis was not severe at autopsy. The elevated transaminase level is unusual on the basis of hepatic congestion alone.[20] The variations in the transaminase concentration did not parallel the degree of congestive failure, having fallen to normal before death at a time when congestive failure was most severe.

Case 2 (fig. 3) F. F., an 11-year-old white boy, had his first attack of rheumatic fever three years prior to admission and a second attack occurred four months prior to admission. When he was admitted to Irvington House, his disease was characterized by fever, polyarthritis, elevation of the sedimentation rate and C-reactive protein, and a prolonged P-R interval and abnormal T waves in the electrocardiogram. While under observation at Irvington House, pericarditis developed and the patient was treated with cortisone for eight weeks. Following treatment no residual evidence of cardiac disease could be demonstrated.

However, his disease relapsed and he developed chest pain, dyspnea, temperature of 104 F., tachycardia and hepatomegaly. The heart became enlarged with distant sounds but no murmurs. The chest x-ray films showed a markedly enlarged cardiac silhouette compatible with a pericardial effusion. The cardiac pulsations were diminished. The cardiothoracic index was 14.1/24.1. The T waves were inverted in leads I, II, III, aV_L, aV_F and V_1 through V_6.

Following the administration of 5.3 Gm. of aspirin daily, the temperature, sedimentation rate, C-reaction protein and heart size returned to normal in eight days. During the second hospital week a faint murmur of aortic insufficiency appeared. The P-R interval became prolonged and the T waves became "coved" and more deeply inverted. The liver function tests were normal. At this time the sedimentation rate, C-reaction protein and temperature were normal, but the serum transaminase rose to levels between 120 to 240 units for three weeks. Coincident with the administration of cortisone, the concentration of the enzyme rapidly fell to normal levels and remained so during convalescence. There was no relapse of clinical symptoms when cortisone was withdrawn. After four months, his cardiac status was unremarkable except that a faint aortic diastolic murmur was inconstantly heard. The electrocardiogram findings were within normal limits.

Comment. This patient had severe, active carditis treated with aspirin, then with cortisone. Initially the serum glutamic oxalacetic transaminase was normal in the presence of obvious clinical and laboratory evidence of acute inflammatory disease. Despite the rapid return to normal of all signs of acute inflammation, the serum transaminase rose to levels three to six times the upper limit of normal,

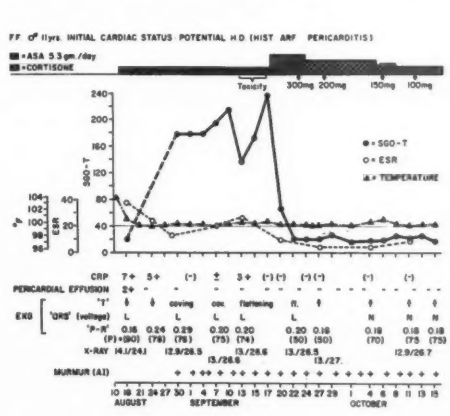


FIG. 3. The elevated serum glutamic oxalacetic transaminase in an 11 year old boy with acute rheumatic pancarditis. (F. F., case 2) is shown. Note the rapid fall of serum glutamic oxalacetic transaminase to normal coincident with the administration of cortisone.

returning to normal limits coincident with the administration of cortisone.

Case 3 (fig. 4) L. DeT. was a ten year-old white boy with severe, chronically active rheumatic carditis of more than two years duration. He had had repeated bouts of congestive heart failure, pericarditis with effusion, intermittent fever and persistently abnormal CRP and ESR. His heart was markedly enlarged. The murmurs of mitral stenosis, mitral insufficiency and aortic insufficiency were heard. During the period that determinations of SGO-T were made, he had two episodes of moderately severe congestive failure

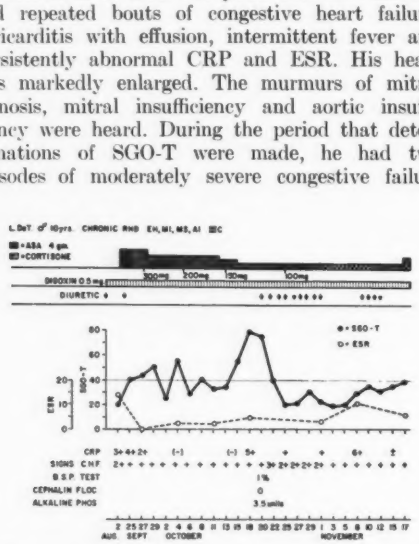


FIG. 4. The course of a 10 year old boy (L. DeT., case 3) with severe, chronically active carditis and congestive heart failure is illustrated. The serum glutamic oxalacetic transaminase was elevated intermittently but showed no relationship to the degree of congestive failure, the laboratory signs of inflammation, or therapy with cortisone.

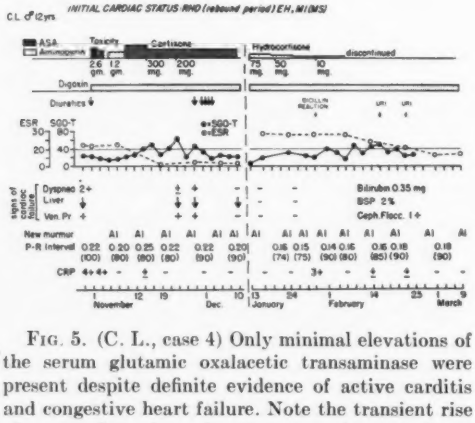


FIG. 5. (C. L., case 4) Only minimal elevations of the serum glutamic oxalacetic transaminase were present despite definite evidence of active carditis and congestive heart failure. Note the transient rise of serum glutamic oxalacetic transaminase during a period of mild laboratory rebound after discontinuation of cortisone.

requiring the administration of mercurial diuretics and Digoxin. In spite of suppressive therapy with aspirin, then cortisone, the C-reactive protein was intermittently strongly positive. The sedimentation rate remained normal. The serum glutamic oxalacetic transaminase was elevated on several occasions during September when congestive heart failure was mild and the CRP was 2 to 4 mm. and was again elevated during October prior to an episode of severe congestive heart failure. The maximum rise of the transaminase to 76 units was seen in October when the CRP was 5 mm. The relationship of the elevated transaminase to a rise in CRP was not consistent, since during November the transaminase was normal although one C-reactive protein was 6 mm. Liver function studies were normal.

Comment. This patient had obviously active, severe, chronic rheumatic heart disease. While the patient was receiving cortisone, the SGO-T was intermittently abnormal with no consistent relationship to the severity of congestive heart failure or to the amount of CRP in the serum.

Case 4 (fig. 5) C. L., a 12 year old Negro boy admitted to Irvington House on Oct. 25, 1954 from another hospital, had been given cortisone there for an attack of acute carditis, characterized by an enlarged heart, dyspnea, fever, murmurs of mitral stenosis and insufficiency, tachycardia, a prolonged P-R interval and the development of pericarditis and congestive heart failure while under treatment. One month previously he had received aspirin for an attack of acute polyarthritis. While evaluating his status at Irvington House in October, cortisone was discontinued and the patient soon developed severe congestive heart failure again. He required treatment with digoxin, mercurial diuretics and aspirin. The sedimentation rate was 25 mm. in 1 hour, C-reactive protein 4 mm., and the electrocardiogram showed a P-R interval of 0.22 second at a heart rate of 100 per minute. The murmur of aortic insufficiency then appeared. Despite this evidence of acute carditis, the serum glutamic oxalacetic transaminase was normal. Toxicity to aspirin and aminopyrine ensued and cortisone therapy was reinstituted. During cortisone therapy late in November, the transaminase in the serum rose to 54 units transiently. At that time mild congestive heart failure reappeared, perhaps partly the result of fluid retention from cortisone. The C-reactive protein and sedimentation rate were normal at the time the transaminase was elevated. After cortisone therapy was withdrawn, there was a temporary reappearance of C-reactive protein and an elevation of the erythrocyte sedimentation rate. Coincident

with this, there was a mild transient elevation of the serum transaminase to 50 units.

Comment. This patient had severe acute carditis which was not correlated with an elevation of the glutamic oxalacetic transaminase of the serum when his symptoms were of maximum severity, his sedimentation rate elevated and his C-reactive protein strongly positive. The first transient rise in the transaminase of the serum that was observed occurred later in the course of the disease, while he was being treated with cortisone. At this time, the sedimentation rate and C-reactive protein were normal. The second rise occurred after cortisone withdrawal when C-reactive protein and sedimentation rate were again abnormal.

Case 5 (fig. 6) G. M., a 14-year-old white boy, gave a history of recurrent polyarthritis for five years. In May 1954, two weeks following cessation of prophylactic penicillin treatment, polyarthritis reappeared. The erythrocyte sedimentation rate and C-reactive protein were elevated. Apical diastolic and systolic murmurs were heard.

In August, therapy with aspirin was initiated at another hospital. The patient was transferred to Irvington House for further observation and the aspirin was discontinued. One day after admission, polyarthralgia reappeared. The temperature was 102 F. The cardiac murmurs became more intense. During October, his polyarthralgia persisted while he was receiving 30 mg. of hydrocortisone daily. This symptom disappeared in November when the hydrocortisone was increased to 50 mg. daily. The heart size enlarged progressively.

The sedimentation rate was persistently elevated to as high as 40 mm. in 1 hour and the C-reactive protein was intermittently positive to as much as 4 mm. The glutamic oxalacetic transaminase of the serum was never elevated.

Comment. This patient had unequivocal evidence of acute carditis, although less severe than the preceding cases. There were never any manifestations of congestive heart failure. The serum transaminase was never elevated either during the course of cortisone therapy or after its withdrawal despite the laboratory evidences of acute inflammatory disease.

Case 6 (fig. 7) J. B. represents the one rheumatic fever patient who showed elevations in the serum glutamic oxalacetic transaminase but did not have definite evidence of active carditis. He was a 10-year-old Negro boy with a history of migratory polyarthritis for two months. His arthritis had been suppressed by aspirin which was discontinued one month prior to this admission.

On the day of admission, October 8, he was noted to have a nasopharyngitis. The throat culture was positive for group A, β-hemolytic streptococci. He then complained of mild polyarthralgia. On October 11 he developed frank polyarthritis. There was no clinical evidence of involvement of the heart except for an apical systolic murmur of grade I to II intensity considered to be of questionable significance. No diastolic murmurs were heard. The erythrocyte sedimentation rate was 42 mm. in 1 hour and the C-reactive protein, 8 mm. There was prompt remission of the arthritis and return of the temperature and C-reactive protein to normal after the administration of aspirin in doses

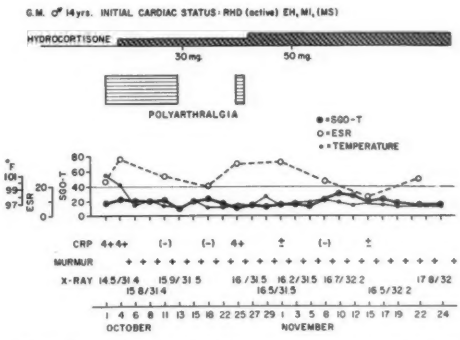


FIG. 6. (G. M., Case 5) Serum glutamic oxalacetic transaminase was consistently normal in this 14 year old boy despite rheumatic carditis of moderate severity.

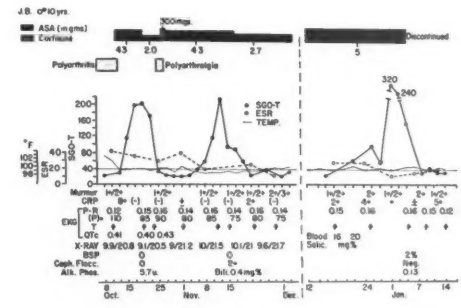


FIG. 7. (J. B., case 6) Note the three peaks of serum glutamic oxalacetic transaminase activity in this 10 year old boy with polyarthritis. This was the only case reported in this series in which definite evidence of cardiac involvement could not be established when the serum glutamic oxalacetic transaminase was elevated.

of 4.3 Gm. daily. The sedimentation rate returned to normal more slowly.

The patient cooperated poorly and received his salicylates irregularly. This was reflected by fluctuating blood salicylate concentrations, falling to as low as 4 mg. per 100 cc. on one occasion. Polyarthralgia reappeared transiently (October 22) and lasted three days. Liver function tests were essentially normal although the cephalin flocculation was 2 plus on one occasion. At no time were the electrocardiogram or cardiac silhouette on x-ray films abnormal. The only suggestive clinical evidence of acute carditis was a slight alteration in the apical systolic murmur which assumed a somewhat harsher quality of grade II to III intensity for one week in December. The C-reactive protein was intermittently positive after the arthritis had disappeared.

Three marked peaks of serum transaminase elevation were observed, the first closely following the attack of polyarthritis, the second and third after the patient had long been completely asymptomatic except for a mild upper respiratory infection. The glutamic oxalacetic transaminase was normal on admission when the temperature, sedimentation rate and C-reactive protein were markedly abnormal. When the temperature, sedimentation rate and C-reactive protein had returned to normal, the serum level of the enzyme rose to 200 units. At the time of the second peak of the serum transaminase, the temperature, sedimentation rate and C-reactive protein were again normal.

TABLE 2.—*Microscopic Findings: Incidence of Elevated Serum Glutamic Oxalacetic Transaminase (SGO-T)*

	Total Number of Patients		Number of Patients Abnormal	
A. Acute Inflammation	10		5	
(a) Aschoff Nodules		7		3
(b) Round Cell Infiltration		4		2
(c) Active Myocardial Cell Necrosis		1		1
(d) Fibrinoid Degeneration of Collagen		4		3
B. No Evidence of Inflammation	5		1	
(a) Replacement of Myocardial Fibres		1		1

Microscopic evidence of myocardial hypertrophy was present in all cases; 27 sera were analyzed of which 12 were abnormal.

This table analyzes the correlation of the serum glutamic oxalacetic transaminase with the microscopic findings in autopsy and atrial biopsy material.

During the period of the third elevation of the serum transaminase, the C-reactive protein rose to 5 mm. and the sedimentation rate to 28 mm. in 1 hour.

Cortisone was administered in a dose of 300 mg. on October 26 in an attempt to determine its effect on the serum concentration of the glutamic oxalacetic transaminase. However, the results of the experiment could not be interpreted because the control serum obtained immediately prior to therapy but analyzed the next day, showed that the concentration of the enzyme in the serum had already returned to normal.

Comment. This case of frank polyarthritis is of particular interest in that it is the only case in this series in which the transaminase of the serum was repeatedly abnormal despite the absence of previously known rheumatic heart disease or definite evidence of clinical cardiac involvement. There was, however, a transient change in the quality and intensity of the apical systolic murmur and there was laboratory evidence of persistent inflammation as manifested by the intermittently positive C-reactive protein. Polyarthritis, per se, did not seem to be related to the elevations of the serum glutamic oxalacetic transaminase, since the second and third peaks of enzyme concentration occurred when no polyarthritis was present.

One patient with known rheumatic heart disease showed an elevated transaminase level of 70 units on one occasion during the course of virus pneumonia. At this time, his electrocardiogram showed abnormal T-waves which reverted to normal with the subsidence of the pneumonia. We believe it is likely that this patient had the mild myocarditis occasionally seen during virus infections.[17]

Correlation with Microscopic Findings

Sections of the heart were available for microscopic study in 15 patients (table 2). This material consisted of biopsies of atrial appendages obtained at the time of mitral valulotomy in 12 patients and autopsy material in 3 patients. Only one of the patients (C. M., fig. 2, case 1) included in table 2 was also included in table 1. The remainder of the patients were excluded from table 1 because only one or two sera were obtained prior to surgery or death. This was considered to be

an inadequate sampling in view of some of the transient abnormalities noted in other patients in whom bleedings were performed three times weekly for many months.

Sera obtained after surgery were not included. It has been noted that the serum level of transaminase invariably rises after chest surgery in animals[4] or patients,[20] presumably as a result of trauma to the pectoralis and intercostal muscles. Hence, any abnormality in the glutamic oxalacetic transaminase of the serum during the first two weeks following chest surgery is influenced by the skeletal muscle damage from surgical trauma. Patients were listed in table 2 according to microscopic findings of the pathologist before the transaminase values were known.

Despite the small number of analyses and the probability that atrial appendage biopsies will be seen to have Aschoff nodules in only approximately 75 per cent of patients subsequently shown to have Aschoff nodules elsewhere in the heart,[19] table 2 shows a high incidence of elevated transaminase determinations in those patients with microscopic evidence of acute inflammation. Criteria for microscopic evidence of an acute inflammatory process in the heart included the presence of any of the following: (1) Aschoff nodules, (2) infiltration with round cells or polymorphonuclear leucocytes, (3) fibrinoid degeneration of collagen and (4) active myocardial fiber necrosis. Myocardial cell hypertrophy was present in all 15 patients and was not considered evidence of active disease.

Five of the 10 patients with microscopic evidence of acute inflammation showed an abnormality of serum transaminase within 1 to 5 days before the pathologic specimen was obtained. Only 1 of the 5 patients without microscopic evidence of inflammation showed an abnormal serum level of transaminase. This patient had extensive fibrosis of the myocardium, although no acute fiber degeneration could be demonstrated.

Discussion

It appears most likely from analysis of these clinical and pathologic data that abnormalities of serum glutamic oxalacetic transaminase in rheumatic fever reflect myocardial damage. The high incidence of positive tests, in the patients with definitely or questionably active carditis, contrasts with the frequency of negative tests in the groups of patients with inactive rheumatic fever, active rheumatic fever without evidence of carditis, active joint involvement in rheumatoid arthritis and many other inflammatory diseases in which heart, liver and skeletal muscle are uninvolved. No marked rise in transaminase has been observed following pulmonary infarction.[20]

Liver function when tested was normal in all the patients in the series except one (C. M.). Although skeletal muscle damage as seen in dermatomyositis will cause an elevation in serum glutamic oxalacetic transaminase[20], this diagnosis was not suspected in any of the patients included in this study. The influence of mercuhydrin, digitalis and aspirin administration upon the serum level of glutamic oxalacetic transaminase was studied in a group of nonrheumatic adults. No effect of these drugs was noted.

Previous observations have shown that a rise in the transaminase level may occur following experimental production of necrosis of as little as 1 Gm. of myocardial tissue.[3] It was further demonstrated that a necrotic area of myocardium may contain less than 10 per cent of the concentration of transaminase in normal myocardium from the same animal.

Although the number of determinations performed in the patients included in table 2 is small, it can be seen that 50 per cent of patients with microscopic evidence of acute myocardial inflammation due to rheumatic fever showed abnormalities of serum glutamic oxalacetic transaminase. The one patient without evidence of active inflammation, but with a high serum transaminase level, showed patchy fibrous replacement of myocardial fibers in the amputated auricular appendage.

In view of the belief of some[21] that the Aschoff nodule arises from the myocardial cell itself, it is of some interest that there was no evidence in this limited series of a higher incidence of abnormal serum levels of glutamic oxalacetic transaminase in the patients with Aschoff nodules than in those with other evidences of an inflammatory process, such as

round cell infiltration or fibrinoid degeneration of collagen.

The relationship of fluctuations in the serum transaminase to variations in the clinical course of the patients is not clear. Although the appearance of congestive heart failure in children with acute rheumatic carditis is considered to be a sign of severe myocardial involvement, the serum level of the enzyme was not consistently elevated during these episodes in our group of patients. One of the nine patients in this category (table 1, group I,a) showed no elevation of the serum transaminase at any time during his hospital course.

In addition, the serum glutamic oxalacetic transaminase did not correlate consistently with alterations in the acute phase reactants. This suggests that the degree of functional impairment and inflammation of the myocardium in the rheumatic process may not be the same as the degree of injury or necrosis of myocardial fibers as measured by serum levels of transaminase. It suggests that during the course of the acute interstitial inflammatory process in the myocardium, myocardial fiber damage may supervene. Intermittent elevations of transaminase in the serum may reflect periods when damage to the myocardial fiber is occurring. The effect of the acute inflammatory process may be partly toxic causing functional impairment of the myocardium without concomitant liberation of transaminase.

Some of the observations during cortisone and aspirin therapy support this concept, since in a number of patients striking abnormalities of serum glutamic oxalacetic transaminase were noted at a time when the nonspecific indices of inflammation had been suppressed. This again indicates that elevations of transaminase in the serum and the nonspecific acute phase reactants are measurements of different aspects of the rheumatic process.

The influence of therapy with cortisone and salicylates upon alterations in the serum transaminase is unclear. Because of the severity of the illness in the patients studied, it was not feasible to compare the behavior of serum transaminase in treated and untreated groups. It is apparent, however, that despite the administration of antirheumatic therapy with relatively large doses of cortisone, elevations in serum transaminase occurred. This was true even when the laboratory signs of systemic inflammation were suppressed. This observation may indicate that the powerful anti-inflammatory effects of cortisone do not completely prevent myocardial injury and is consistent with the lack of curative effect of these compounds upon chronic rheumatic myocarditis.

The question of whether steroid or salicylate therapy may influence the serum level of glutamic oxalacetic transaminase is of considerable theoretic and practical importance. At present, the index of "adequate" antirheumatic therapy is considered to be suppression of laboratory evidence of inflammation as well as a satisfactory clinical response. However, the ultimate goal in treating rheumatic fever is protection of the patient against permanent cardiac injury. If the concentration of transaminase in the serum is an index of myocardial fiber injury, as suggested above, it is possible that an attempt should be made to increase or continue antirheumatic therapy until the serum transaminase returns to normal levels.

The normal transaminase concentrations in the spinal fluid in the three patients with chorea who were studied are not surprising in view of the absence of changes in the cerebrospinal fluid in chorea usually associated with inflammatory disease.[22] The most common microscopic finding in the brain is perivascular infiltration with round cells. No necrosis of brain tissue is seen, hence a release of transaminase would not be expected.

In a total of six rheumatic fever patients, simultaneous measurements of transaminase in the spinal fluid and blood were performed. The ratio of serum concentration to spinal fluid concentration ranged from 2:1 to 5:1, indicating that a barrier to free diffusion of transaminase is present at the subarachnoid membrane.

Summary

Serum glutamic oxalacetic transaminase (SGO-T) was studied in 64 patients in various

stages of rheumatic fever and in 15 patients, either at autopsy or in whom atrial biopsy was performed during mitral commissurotomy.

Elevations in the level of this serum enzyme occurred with greatest frequency in patients with clinical or histologic evidence of active rheumatic carditis. Normal values were found in rheumatic patients without clinical evidence of active cardiac involvement. The serum level was within normal limits in all patients after the acute rheumatic process subsided.

Although frequently high, the levels of serum glutamic oxalacetic transaminase were not consistently elevated in patients with active carditis and did not follow the clinical course of the disease closely.

The effect of aspirin or cortisone upon the concentration of transaminase in the serum could not be evaluated clearly in the absence of a control group. Some patients with severe, protracted carditis continued to have an elevated serum level of glutamic oxalacetic transaminase despite the prolonged administration of relatively large doses of cortisone.

The probable relationship of increased transaminase activity to myocardial damage in rheumatic carditis is discussed.

Acknowledgment

The authors wish to thank Dr. David P. Barr, Professor of Medicine of Cornell University Medical College, Dr. Thomas P. Almy, Director of the Second (Cornell) Medical Division of Bellevue Hospital and Dr. Rulon W. Rawson, Chief of Medicine, Memorial Center for Cancer and Allied Diseases, for their generosity in making some of the clinical material reported here available to us.

The technical assistance of Shirley Baty, Patricia Van Dawson, Martin Podgainy, Alfred Friedman and Leight Collins is also acknowledged with thanks.

Summario in Interlingua

Esseva studiate in 64 patientes con febre rheumatic le variationes in le concentration seral del enzyma transaminase oxalacetic glutamic. Elevationes esseva notate in 17 ex 28 patientes con carditis de definite o dubitose activitate e transientemente in un patiente rheumatic con myocarditis viral. Con le exception de un patiente qui habeva polyarthritis e signos equivoc de un acute involvimento cardiac, le concentrationes seral esseva normal durante rheumatic manifestationes noncardiac e in carditis inactive. Il non habeva ulle relation con temperatura, rapiditate de sedimentation, conto leucocytic, o proteina C-reactive. Il es probabile que un intermittente necrosis de fibras myocardial causa iste augmentate concentrationes seral de transaminase.

REFERENCES

[1] Awapara, J. and Seale, H.: Distribution of transaminase in rat organs. J. Biol. Chem. **194:** 497, 1952.

[2] Cammarata, P. S. and Cohen, P. P.: The scope of transamination reaction in animal tissues. J. Biol. Chem. **187:** 439, 1950.

[3] Nydick, I., Wróblewski, F. and LaDue, J. S.: Alterations of serum glutamic oxalacetic transaminase (SGO-T) following graded myocardial infarction in dogs. Circulation **12:** 161, 1955.

[4] LaDue, J. S., Wróblewski, F. and Karmen, A.: Serum glutamic oxalacetic transaminase activity in human acute transmural myocardial infarction. Science **120:** 497, 1954.

[5] Wróblewski, F. and LaDue, J. S.: The significance of the serum glutamic oxalacetic transaminase activity following acute myocardial infarction. Circulation **11:** 811, 1955.

[6] Karmen, A., Wróblewski, F. and LaDue, J. S.: Transaminase activity in human blood. J. Clin. Invest. **34:** 126, 1955.

[7] Agress, C. M., Jacobs, H. I., Glassner, H. G., Lederer, M., Clark, W., Wróblewski, F., Karmen, A. and LaDue, J. S.: Serum transaminase levels in experimental myocardial infarction. Circulation **11:** 711, 1955.

[8] Robertson, T., Kellner, A. and Thal, A.: Widespread focal myocarditis induced in rabbits by means of papain solutions injected intravenously. Am. J. Path. **27:** 753, 1951.

[9] Schweid, A. and Kellner, A.: Personal communication.

[10] LaDue, J. S. and Wróblewski, F.: Serum glutamic oxalacetic transaminase activity as an index of liver cell injury. Ann. Int. Med. **43:** 345, 1955.

[11] Molander, D. W., Wróblewski, F. and LaDue, J. S.: Transaminase compared with cholinesterase and alkaline phosphatase as an index of hepatocellular integrity. Clinical Research Proceedings **3:** 20, 1955.

[12] Price, J. S., Wróblewski, F. and LaDue, J. S.: Unpublished observation.

[13] Stollerman, G. H., Glick, S., Patel, D., Hirschfeld, I. and Rusoff, J.: Determination of C-reactive protein as a guide to the treatment and management of rheumatic fever. Am. J. Med. **15:** 645, 1953.

[14] Fischel, E. E., Pauli, R. H. and Lesh, J.: Serological studies in the rheumatic state. J. Clin. Invest. **28:** 1172, 1949.

[15] Anderson, H. C. and McCarty, M.: Determination of C-reactive protein in the blood as a measure of the activity of the disease process in acute rheumatic fever. Am. J. Med. **8:** 445, 1950.

[16] Jones, T. D.: The diagnosis of rheumatic fever. J.A.M.A. **126:** 481, 1944.

[17] Gore, I. and Saphir, O.: Myocarditis, a classification of 1402 cases. Am. Heart J. **34:** 827, 1947.

[18] Stollerman, G. H., Lewis, A. F., Taranta, A. and Schultz, I.: The relationship of the immune response to group A streptococci to the course of acute, chronic and recurrent rheumatic fever. In preparation.

[19] Kuschner, M. and Levieff, L.: Correlation between active rheumatic lesions in the left auricular appendage and elsewhere in the heart. Am. J. M. Sc. **226:** 209, 1953.

[20] Nydick, I., Wróblewski, F. and LaDue, J. S. Unpublished observation.

[21] Murphy, G. E.: The Histopathology of Rheumatic Fever. *In*, Rheumatic Fever, L. Thomas, ed. Minneapolis, University of Minnesota Press, 1951, p. 28.

[22] Taranta, A. and Stollerman, G. H.: Unpublished observations.

Costophrenic Septal Lines in Pulmonary Venous Hypertension

By André J. Bruwer, M.B., Ch.B., F. Henry Ellis, Jr., M.D. and John W. Kirklin, M.D.

On the thoracic roentgenograms of patients with mitral stenosis, costophrenic septal lines are frequently seen. These lines are a sign of pulmonary venous hypertension. They were not seen in a representative group of patients with pulmonary arterial hypertension but without pulmonary venous hypertension.

PROGRESS in the surgical management of congenital and acquired cardiovascular diseases has stimulated many branches of medicine. Roentgenology of the cardiovascular system is one of the diagnostic fields that has profited by these advances. One of the interesting and curious findings in roentgenograms of the thorax of patients with mitral heart disease has been the presence of fine, short, straight linear densities in the costophrenic regions (figs. 1 and 2). Although these lines are not specific for mitral heart disease, their preponderant presence in this condition stimulated us to review the roentgenograms at the Mayo Clinic of 152 surgical cases of mitral stenosis.

Definition

The lines with which this paper deals have been variously described as "lines B of Kerley,"[1] "horizontal lines,"[2] "linear x-ray shadows"[3] and "septal lines."[4] They are reported to occur occasionally in association with a number of conditions including acute and chronic pulmonary congestion, severe mitral stenosis,[3] pulmonary hemosiderosis in the absence of congestion,[3] pneumoconiosis, diffuse pulmonary fibrosis and lymphogenous pulmonary metastasis. The lines usually are seen best in the costophrenic angles and better on the right side than on the left. The posteroanterior view is the best, but occasionally an oblique or lateral view will show them to advantage. They run perpendicular to the pleural surface. As a rule, a single line will be of the same thickness throughout, but if it tapers, its broadest end tends to be based on the visceral pleura. The lines vary in number from 2 or 3 to 10 or 15. They extend from 2 to 4 inches upward from the costophrenic angle and vary in thickness from a hairline to 2 mm. in diameter. Often they are spaced from 0.5 to 1 cm. apart. They may remain unchanged after mitral commissurotomy, or they may disappear. Sometimes they disappear as early as the first day after mitral commissurotomy.

Cautious interpretation of these lines is advisable, so that they will not be confused with linear fibrosis following inflammatory processes or with peripheral arborization of the pulmonary vascular tree (fig. 3).

Pathogenesis

Some authors have related these lines to "pulmonary hypertension in patients with mitral stenosis,"[2] while others have considered them as "radiological signs in pulmonary hypertension."[5] The latter authors have stated that "in general, the lines are present only when there is at least moderate pulmonary hypertension."

Fleischner and Reiner,[3] basing their interpretations on Gough and Wentworth's method[6] of holoptic microtome sections of lungs, present evidence that the lines are sometimes due to peripheral interlobular septa which have been rendered visible on roentgenograms, after hemosiderin has been deposited in or adjacent to them. Such lines tend to be relatively permanent. Similar, but transient, lines are thought to be due to linear accumulations of fluid on the septa, appearing during periods of pulmonary congestion and disappearing as

From the Mayo Clinic and Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

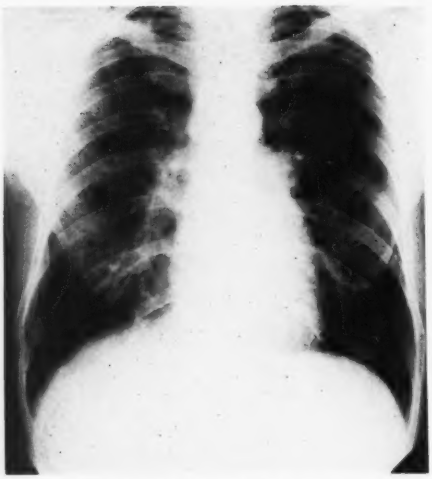


FIG. 1. Postero anterior view in a case of mitral stenosis showing costophrenic septal lines.

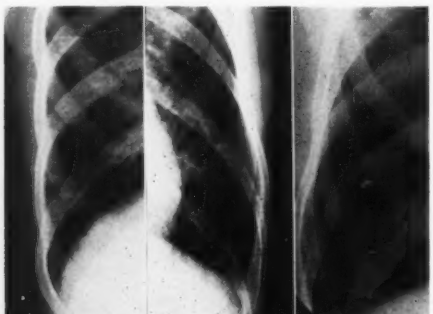


FIG. 3*a*, *b* and *c*. Localized views of a costophrenic angle in three cases of mitral stenosis, showing costophrenic septal lines.

pulmonary congestion is overcome. Kerley[7] considered the lines to be due to engorged subpleural lymphatics.

PRESENT STUDY

We have examined roentgenograms of 152 cases of mitral stenosis in which the patients had undergone mitral commissurotomy. The study was made specifically for the presence of costophrenic septal lines. As in the study by Carmichael and associates,[5] doubtful cases were regarded as negative. In 51 of the 152

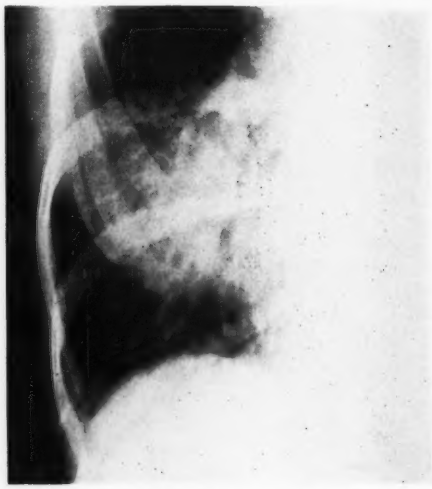


FIG. 2. A case of ventricular septal defect showing peripheral arborization of the pulmonary arteries. This should not be confused with costophrenic septal lines.

cases of mitral stenosis, the lines were present. In view of work, previously referred to, relating the lines to pulmonary hypertension, our patients having mitral stenosis who had undergone cardiac catheterization were analyzed in regard to the presence or absence of lines. Furthermore, roentgenograms in 65 cases of pulmonary hypertension due to causes other than mitral stenosis were examined for the presence of costophrenic septal lines. We were impressed with the fact that the costophrenic septal lines frequently disappeared soon after mitral commissurotomy, whereas in other cases they remained unchanged after mitral commissurotomy. Cases in which a follow-up study of at least six months was made were therefore analyzed in an attempt to relate disappearance of the lines to prognosis.

RELATION OF MEAN PULMONARY-TRUNK PRESSURES TO COSTOPHRENIC SEPTAL LINES

In 46 of our cases of mitral stenosis, mean values for pulmonary-trunk pressures were available. We arbitrarily divided our cases into the group with mean pressures below

60 mm. Hg and those with mean pressures above 60 mm. Hg. It was found that 14 of the 46 patients had mean pressures of more than 60 mm. Hg; of the 14, 8 had costophrenic septal lines, whereas 6 did not. Thirty-two of the 46 patients had mean pulmonary-trunk pressures of less than 60 mm. Hg; 12 had lines, whereas 20 did not show lines (table 1). Our findings contrast with those of Carmichael and associates, who noted lines in 100 per cent (18 cases) of their patients having mean pressures of more than 60 mm. Hg and in only 18 per cent (five cases) of those having mean pulmonary-trunk pressures of less than 60 mm. Hg.

TABLE 1.—*Relationship of Mean Pulmonary Trunk Pressures to Presence of Costophrenic Septal Lines on Roentgenograms of the Thorax*

Mean Pulmonary-Trunk Pressures	Lines Present		Lines Absent	
	Cases	%	Cases	%
More than 60 mm. Hg....	8	57	6	43
Less than 60 mm. Hg....	12	37	20	63

TABLE 2.—*Relationship of Degree of Pulmonary Hypertension to Presence of Costophrenic Septal Lines on Roentgenograms of the Thorax*

Pulmonary Hypertension, Degree	Costophrenic Septal Lines	
	Present, cases	Absent, cases
Mild, 30–49 mm. Hg.....	2	8
Moderate, 50–69 mm. Hg.....	7	6
Severe, more than 70 mm. Hg.....	17	12

TABLE 3.—*Relationship of Mean Pulmonary Wedge Pressures to Presence of Costophrenic Septal Lines on Roentgenograms of Thorax*

Mean Wedge Pressures	Costophrenic Septal Lines			
	Present, per cent of cases		Absent, per cent of cases	
	Mayo Clinic series	Series of Carmichael and associates[5]	Mayo Clinic series	Series of Carmichael and associates[5]
29 mm. Hg. and over	55	86	45	14
Less than 29 mm. Hg.*	30	7.5	70	92.5

* The figure, 29 mm. Hg., was arbitrarily chosen for convenience of comparison. In all our cases the mean wedge pressures were considered to be elevated.

Pulmonary-Artery Systolic Pressure and Costophrenic Septal Lines

Whitaker and Lodge[2] found that costophrenic septal lines were present in 6 of 8 patients having severe pulmonary hypertension, in 8 of 10 patients having moderate pulmonary hypertension and in 1 of 7 patients having mild pulmonary hypertension. In order to compare our cases with their group, we arbitrarily divided our cases into mild, moderate and severe pulmonary hypertension when the systolic pressures in the pulmonary trunk were respectively 30 to 49 mm. Hg, 50 to 69 mm. Hg and 70 mm. Hg or more. Of the 10 patients having mild pulmonary hypertension, two had lines; of 13 having moderate pulmonary hypertension, 7 had lines; while of 29 having severe pulmonary hypertension, 17 had lines (table 2).

Relation of Mean Wedge Pressures to Costophrenic Septal Lines

We were able to obtain figures for mean wedge pressures in 38 cases to compare with the group of 28 cases of mean wedge pressures presented by Carmichael and co-workers. Here again, they found a closer relation between the height of the mean wedge pressure and the presence of lines (table 3). In our group there was no correlation between the height of the mean wedge pressure and the distinctness, number or size of the lines. In fact, we had graded the lines as "marked" in only three of 38 cases, and in all three the mean wedge pressures were less than the arbitrary dividing line of 29 mm. Hg. The mean wedge pressures in these three cases were 24, 25 and 28 mm. Hg, respectively.

Relation of Postcommissurotomy Status to Costophrenic Septal Lines

An attempt was made to correlate the status of the lines with the clinical result six months or more after surgical intervention. All nine patients in whom lines disappeared after operation had results graded as "excellent." Seven of 11 patients in whom the lines had persisted after operation had excellent results; two had died and two were

TABLE 4.—*Pulmonary Hypertension in Conditions Other Than Mitral Stenosis**

Defect	Cases
Ventricular s.d.	22
Ventricular s.d. and atrial s.d.	1
Atrial s.d.	15
A.V. commune	1
P.D.A.	14
P.D.A. and atrial s.d.	2
Idiopath. pulmon. hypertens.	8
Pulmonary fibrosis	1
Pericarditis	1
Total	65

* Pulmonary arterial hypertension had been proved by cardiac catheterization but pulmonary venous hypertension was not a characteristic feature. In none of these cases were costophrenic septal lines seen on roentgenograms of the thorax.

s.d. = septal defect.
A.V. = atrioventricularis.
P.D.A. = patent ductus arteriosus.

regarded as failures. If any judgment can be made on such a small group, it would be to suggest that among those patients who had costophrenic septal lines which disappeared after operation, the prognosis would appear to be excellent.

Of further interest in regard to the patients who had died in the first year after operation was the finding that death seemed to be more likely in the group in which we had categorized the lines as being "marked" before operation than in the group in which they had been graded as "slight." Many more cases will have to be studied, however, before any valid conclusions can be drawn.

Pulmonary Hypertension in Conditions Other Than Mitral Heart Disease

As has been stated before, we found that a third of our patients who underwent operation for mitral stenosis had costophrenic septal lines. In order to determine whether the lines are related to conditions in which pulmonary venous hypertension is a characteristic feature, rather than to conditions in which pulmonary arterial hypertension occurs without necessarily being associated with pulmonary venous hypertension, we examined the roentgenograms of 65 patients in the latter category. None of the roentgenograms of these patients showed septal lines (table 4).

In addition, the roentgenograms of 20 patients who had emphysema complicated by cor pulmonale, pulmonary hypertension undoubtedly being present, were examined. Not one of the roentgenograms of these patients showed evidence of costophrenic septal lines.

Furthermore, the roentgenograms of 25 patients who had died and who had had calcific aortic stenosis were examined and costophrenic lines were found in those of three; these three patients had had evidence of cardiac failure with an elevated pulmonary venous pressure.

It would appear that these lines occur, for practical purposes, only among patients having pulmonary venous hypertension associated with pulmonary arterial hypertension, and particularly in mitral heart disease, but not in pulmonary hypertension confined to the pulmonary arterial side.

Comment

We found costophrenic septal lines in the thoracic roentgenograms of a third of 152 cases of mitral stenosis. The roentgenograms were taken prior to the patient's operation in each case. Other authors have described these lines in even a higher percentage of cases than we found. The finding of costophrenic septal lines on a roentgenogram becomes, therefore, a valuable roentgenologic sign. Furthermore, in our experience, the only other condition in which these lines have been seen with significant frequency has been in cardiac failure with disease of the aortic valve and evidence of raised pulmonary venous pressure. Contrary to the impression given in the literature, we do not believe that costophrenic septal lines are a sign of pulmonary arterial hypertension. In the examination of roentgenograms of the thorax of 65 patients with pulmonary arterial hypertension (in cases of, for instance, ventricular septal defect, atrial septal defect and others listed in table 4) and 20 patients with cor pulmonale, following emphysema, we did not find examples of costophrenic septal lines.

It is our opinion, therefore, that these lines are more specifically related to pulmonary hypertension involving the pulmonary venous as well as the pulmonary arterial circulation. We did not, however, find a striking correlation between the degree of elevation of pulmonary wedge pressures and the presence of costophrenic septal lines.

If the distended lines of the type that disappear after operation are assumed to be distended lymphatics, as Kerley[7] suggested, the description of the lymphatic drainage of the lung, as presented by Miller,[8] becomes of interest. According to Miller the pulmonary parenchymal lymphatics drain along the pulmonary veins to the hilus of the lung, and from there they drain to the hilar lymph trunks and nodes. The pleural and subpleural lymphatics run in the numerous sublobular septa, and drain over the surface of the lungs to the hilum. One may speculate, therefore, that when the pressure of blood in the pulmonary venous system rises, this interferes with the drainage of the perivenous lymphatics, their tendency then being to drain peripherally and then via the pleural lymphatic route to the hilum. If they become distended enough they may become visible on the roentgenogram.

An alternative, or perhaps an additional, explanation for the prominence of lymphatics in pulmonary venous obstruction, is found in the experiments of Warren and Drinker on dogs.[9] They discovered a greatly increased flow of lymph from cannulated lymphatics of the lung of the dog after mechanical obstruction of the pulmonary veins. They postulated that the increased flow of lymph was due to a combination of pulmonary hypertension and anoxemia causing greater capillary permeability.

Why costophrenic septal lines would be seen best in the lower 3 or 4 inches of the lung is difficult to explain, except that there may be a hydrostatic effect, the portions of the lung that are dependent most of the time being affected the earliest and the most. Furthermore, the suggestion has been made that the lower portions of the lung fields are better supplied with lymphatics than the upper portions.

This theory would explain also why septal lines do not develop among patients with pulmonary arterial hypertension but without pulmonary venous hypertension. Pulmonary lymphatics drain along the veins but not along the pulmonary arteries[8] and, therefore, their central drainage is not interfered with when the pressure rises only on the arterial side. Lymphatic cannulation experiments in induced pulmonary arterial hypertension would be of great interest.

In a small group of patients in whom we correlated the clinical result six months after operation with the disappearance or persistence of lines after operation, it appeared that surgical results were more consistently excellent in the cases in which the lines disappeared than in the cases in which the lines remained. It is possible that the disappearance of lines reflects a lesser degree of pulmonary damage than exists in the patients in whom the lines remain. As has been mentioned before, there is evidence that the permanent lines probably are associated with hemosiderosis.

Summary and Conclusions

We have found costophrenic septal lines a valuable roentgenologic sign of pulmonary venous hypertension. The lines occurred in a third of surgical cases of mitral stenosis at the Mayo Clinic, but we failed to see them in any cases in which pulmonary arterial hypertension originated proximal to the pulmonary capillary bed and in which pulmonary venous hypertension was, therefore, not a characteristic feature.

Although the lines may occur in association with other conditions, the disease with which they are primarily associated is mitral stenosis.

Summario in Interlingua

Le roentgenogramma thoracic de patientes con stenosis mitral exhibi frequentemente lineas septal costophrenic. Iste lineas es un signo de hypertension pulmono-venose. Illos non esseva trovate in un gruppo representative de patientes con hypertension pulmono-arterial sed sin hypertension pulmono-venose.

REFERENCES

[1] Shanks, S. C. and Kerley, P.: A Textbook of X-ray Diagnosis. Ed. 2, Philadelphia, W. B. Saunders Company, 1951, vol. 2, p. 404.

[2] Whitaker, W. and Lodge, T.: The radiological manifestations of pulmonary hypertension in patients with mitral stenosis. J. Fac. Radiologists. **5:** 182, 1954.

[3] Fleischner, F. G. and Reiner, L.: Linear x-ray shadows in acquired pulmonary hemosiderosis and congestion. New England J. Med. **250:** 900, 1954.

[4] Short, D. S.: Radiology of the lung in severe mitral stenosis. Brit. Heart J. **17:** 33, 1955.

[5] Carmichael, J. H. E., Julian, D. G., Jones, G. P. and Wren, E. M.: Radiological signs in pulmonary hypertension: The significance of lines B of Kerley. Brit. J. Radiol. **27:** 393, 1954.

[6] Gough, J. and Wentworth, J. E.: The use of thin sections of entire organs in morbid anatomical studies. J. Roy. Micr. Soc. **69:** 231, 1949.

[7] Kerley, P.: Quoted by Fleischner, F. G., and Reiner, L.[3]

[8] Miller, W. S.: The Lung. Springfield, Charles C Thomas, 1937, p. 209.

[9] Warren, M. F. and Drinker, C. K.: The flow of lymph from the lungs of dogs. Am. J. Physiol. **136:** 207, 1942.

Syndrome of Left Ventricular–Right Atrial Shunt Resulting from High Interventricular Septal Defect Associated with Defective Septal Leaflet of the Tricuspid Valve

By Mildred Stahlman, M.D., Samuel Kaplan, M.D., James A. Helmsworth, M.D., Leland C. Clark, Ph.D. and H. William Scott, Jr., M.D.

Two similar cases of unusual congenital anomalies of the heart are presented, in which there existed a direct communication between the left ventricle and the right auricle through a defect involving the membranous portion of the interventricular septum with defective formation of the medial leaflet of the tricuspid valve. Data obtained at catheterization, operative and postmortem findings are presented in each case. The differential diagnosis of this type of lesion is discussed.

BECAUSE of recent advances in the surgical treatment of defects of the cardiac septa it has become of considerable practical importance to be able to recognize such defects by their clinical manifestations and to localize them accurately by current diagnostic technics. It is usually not difficult to differentiate defects of the atrial septum from ventricular septal defects. However, we have recently observed two children with manifestations of a large left-to-right intracardiac shunt erroneously diagnosed by clinical and catheterization data in each instance as atrial septal defect. Surgical closure under direct vision by open cardiotomy was attempted in each case but without survival. At autopsy, each child was found to have an unusual form of high interventricular septal defect associated with a malformation of the septal leaflet of the tricuspid valve.

Case Reports

*Case 1.** M. Z., a 4 year old white boy, had been under medical observation most of his life. He was the result of an uncomplicated full term pregnancy, delivery was spontaneous and his birth weight was 5 pounds 8 ounces. At the age of 7 weeks he developed a severe respiratory infection characterized by pyrexia, dyspnea and noisy respirations with a prolonged expiratory phase. Three further similar episodes of respiratory infection occurred during the first year of life. At the age of 1 year he had been treated in the Cincinnati Children's Hospital for bronchopneumonia, tonsillitis and left otitis media. Frequent attacks of bronchitis occurred during the second and third years of life complicated by the development of bronchopneumonia on three occasions. One year before death, congestive cardiac failure occurred during a bout of bronchopneumonia. He was treated with digitalis and mercurial diuretics and maintained on a daily dose of 0.05 mg. digitoxin.

The patient's exercise tolerance was always poor but diminished during his fourth year so that he could walk a distance of only 25 yards. He slept poorly because of orthopnea and a persistent nonproductive cough. Cyanosis was not noted at any time, even during the periods of bronchopneumonia and congestive heart failure.

The boy's weight was 26½ pounds, his height 38 inches and he appeared to have been chronically ill. The venous pressure was increased, causing jugular distension 5 cm. above the sternal angle and the venous pulse exhibited a prominent intrinsic "c" wave. The liver edge, which did not pulsate, was 6 cm. below the right costal margin. There was no peripheral edema and there were no adventitious sounds in the lungs. The pulse was small, 90 per minute and regular. The blood pressure in both upper extremities was 94/50 and 110/60 mm. Hg in both legs.

The precordial area bulged markedly. The apical impulse, which was tapping in nature, was maximal in the sixth intercostal space in the left anterior

From the Departments of Pediatrics and Surgery of the Vanderbilt University School of Medicine, Nashville, Tennessee; the University of Cincinnati College of Medicine and the Children's Hospital, Cincinnati; and The Fels Research Institute for the Study of Human Development, Antioch College, Yellow Springs, O.

* Published in part in The Journal of Thoracic Surgery.[1] Permission to reproduce figures 2 and 3 is hereby acknowledged.

axillary line. A coarse systolic thrill was palpable down the left sternal border. A sternal lift was both visible and palpable. A harsh grade IV systolic murmur was heard maximally in the second left parasternal space but radiated down the left sternal border, to the apex and to the back between the scapulae. The second heart sound was widely split but there were no diastolic murmurs. The electrocardiogram showed evidence of incomplete right bundle branch block (RsR′ in V_1). Roentgenographic studies of the chest showed cardiac enlargement mainly involving the right ventricle. The pulmonary artery segment was prominent, the aortic knob inconspicuous and pulmonary overvascularity was evident (fig. 1). There were no abnormal pulsations of the intrapulmonary vessels. Examination of the peripheral blood, urine and erythrocyte sedimentation rate gave normal values. The total blood volume was estimated to be 990 cc. (T-1824 method).

Cardiac catheterization five months before death gave the following results:

	Pressure Systolic/ Diastolic Mean mm. Hg	Oxygen Content (vols. %)
Pulmonary Capillary	—	—
	12	
Pulmonary Artery	92/38	11.8
	56	
Right Ventricle (outflow tract)	92/10	11.7
	43	
Right Ventricle (mid)	92/10	11.8
	43	
Right Atrium (near tricuspid valve)	12/7	11.9
	10	
Right Atrium (mid)	12/7	11.8
	10	
Superior Vena Cava	—	10.0
O_2 capac. 13.4 vol. per 100 cc.	—	

Arter. O_2 sat. 97 per cent.
Pulmonary artery flow 5.8 L. per minute.
Left-to-right shunt 3.1 L. per minute.
Pulmon. arteriolar resistance 604 dyne second $cm.^{-5}$
Rt. ventric. work 6.6 Kg. M./min./M^2.
Rt. atrial pressure curve showed a prominent "c" wave.

The studies suggested the presence of an atrial septal defect. The increased venous pressure with prominent systolic venous pulsations was thought to be due to associated functional tricuspid insufficiency.

It was planned to close the defect surgically with the aid of the Clark extracorporeal pump oxygenator.[1] The patient was anesthetized with Pentothal sodium following which oxygen and ether were given through a closed endotracheal system. Bags of

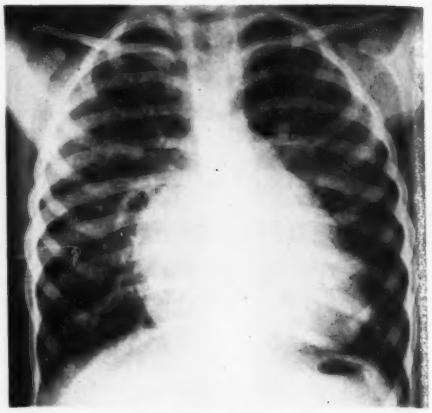


FIG. 1. Case 1. Teleoroentgenogram showing cardiac enlargement, prominent pulmonary artery segment, pulmonary overcirculation and inconspicuous aortic knob.

cracked ice were applied around the trunk and extremities to produce a mild hypothermic stage and the operation was begun after the rectal temperature had been reduced to 90 F. A right anterolateral incision was made and the thoracic cavity entered through the fourth intercostal space. The catheter system for venous drainage included three plastic tubes with multiple perforations. Two of these were inserted via the saphenous veins into the inferior vena cava. The superior vena cava was cannulated through the azygos vein. Arterialized blood was returned through a single cannula placed in the right subclavian artery with its tip in the ascending aorta. The entire extracorporeal system was filled with freshly collected whole blood.

After an intravenous injection of heparin (3 mg. per Kg.) extracorporeal circulation was started and slowly increased to between 1,200 and 1,400 cc. per minute. The superior and inferior vena cava were then occluded. The right atrial wall was opened through an incision extending from the insertion of the superior vena cava to the inferior vena cava (fig. 2). Although the right atrium appeared empty before cardiotomy, the entire area became flooded with a large volume of coronary venous blood within a few minutes. Because of the delay in returning this blood to the extracorporeal circuit, the arterial blood pressure fell to shock levels and did not return to the preoperative level for a period of 50 minutes. The right atrial cardiotomy allowed closure of the complex defect by sutures placed under direct vision. Despite difficulty with the overwhelming coronary venous blood, which was not less than 250 cc. per minute, the right atrium was open for only 17 minutes and the extracorporeal circulation was terminated after a total of 33 minutes.

After the intravenous infusion of protamine sulfate was started, all cannulas were withdrawn, the pleural space was drained and the chest wall closed in the standard manner. Although the boy was able to move his extremities and take sips of water eight hours after operation, he remained anuric and died 16 hours after cardiotomy.

At autopsy the major findings were in the heart. The preoperative diagnosis of atrial septal defect was not confirmed. The basic cardiac anomaly was a high ventricular septal defect of the membranous septum associated with an anomaly of the septal leaflet of the tricuspid valve (fig. 3). The ventricular septal defect had been closed by silk sutures but after their removal, the defect measured 1.5 cm. in diameter. The septal leaflet of the tricuspid valve was very short and incomplete, allowing a direct communication between the left ventricular and right atrial cavities. The right ventricular wall measured 7 mm. and the left 13 mm. in thickness. The circumference of the cardiac valves in millimeters was as follows: tricuspid 105, mitral 85, aortic 60 and pulmonary 60. The myocardium was of normal color and consistency and the pulmonary veins, coronary sinus and venae cavae appeared normal. The ductus arteriosus was obliterated and the aorta was normal. The other positive findings included 90 cc. of blood in the right pleural cavity, some atelectasis of the dorsal portion of both lungs, a small recent infarct of the upper pole of the right kidney, mucosal hemorrhages in the stomach and acute focal colitis. Because the brain was not examined, the possibility of cerebral air embolism could not be excluded.

Case 2. M. H. W. III, a 4 year old white boy, was the result of a full term pregnancy uncomplicated by maternal illness. Delivery was spontaneous and no cyanosis was observed at birth. A cardiac murmur was noted by his attending pediatrician in early infancy. Feedings were taken poorly and his growth pattern was below normal standards. He vomited frequently throughout his first year of life. At the age of 2 years, the boy developed a severe acute respiratory infection characterized by fever, dyspnea and cough which was diagnosed as bronchopneumonia and required hospitalization. Cyanosis was said to be present at this time and he was treated with penicillin and oxygen with disappearance of cyanosis and respiratory symptoms. Subsequently, he showed no cyanosis on exercise and his exercise tolerance was good, although he was said to tire a bit sooner than his siblings. At no time had he shown signs or symptoms of cardiac failure.

On July 28, 1952, at the age of 2½ years, he was admitted to Vanderbilt University Hospital for the first time and cardiac catheterization was unsuccessfully attempted. He was discharged and readmitted on Nov. 5, 1952. At this time cardiac catheterization was successfully performed. Physical examination showed a weight of 25 pounds and

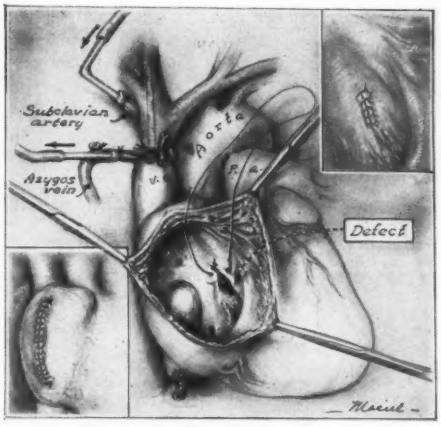


FIG. 2. Case 1. Right atrial cardiotomy showing exposure of the septal defect. Cannulation of the superior vena cava for venous pickup and subclavian artery for arterial return are also indicated.

From J. A. Helmsworth and associates,[1] reproduced by permission of J. Thoracic Surg.

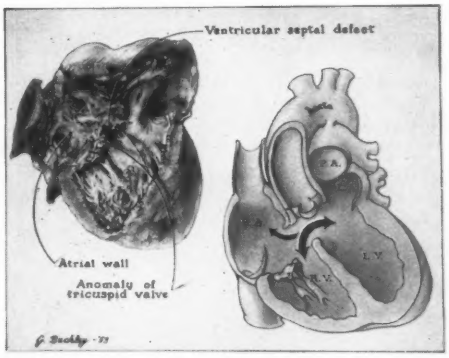


FIG. 3. Case 1. Ventricular septal defect and tricuspid valve anomaly as viewed through the opened right atrium and ventricle.

From J. A. Helmsworth and associates,[1] reproduced by permission.

height of 34 inches. He was an energetic, wiry little boy who was in no distress. There was no evidence of cyanosis of the mucous membrane or clubbing of the fingers. No edema was present and the liver was not palpable. The pulse was full in all extremities and averaged 85 per minute. The blood pressure in both arms was 98/76 mm. Hg and in both legs 104/70. There was a marked precordial bulge associated with a mild pigeon breast deformity. The precordium was overactive and the apical impulse was in the left fifth intercostal space at the anterior axillary line. There was a coarse systolic thrill easily felt over the left lower precordium. A harsh grade IV systolic

murmur was best heard in the left fourth and fifth intercostal spaces parasternally and it was widely transmitted over both left and right sides of the chest, anteriorly, but poorly transmitted to the back. Diastole was clear. The pulmonary second sound was moderately accentuated. There was a regular sinus rhythm. The remainder of the examination was essentially negative.

The electrocardiogram showed right ventricular enlargement and inverted T_1, T_{VL} and T of V_1 through V_6. There was depression of S-T_1, S-T of aV_F, V_4 and V_6. Roentgenographic studies of the chest showed a bizarre configuration. There was fullness of the pulmonary artery region and the right ventricle was markedly enlarged. The right border of the cardiac shadow projected far into the right lung field as a large smooth crescent and pulsations in this region were diminished. The vascularity of the lungs was increased. Examination of the blood, urine and erythrocyte sedimentation rate were within normal limits. Cardiac catheterization was performed and while an attempt was being made to turn the catheter tip into the left pulmonary artery, the sinus mechanism was replaced by atrial fibrillation with a ventricular rate of 200 beats per minute. As this mechanism persisted, the procedure was discontinued with a minimum of catheterization data having been obtained. These data appear below:

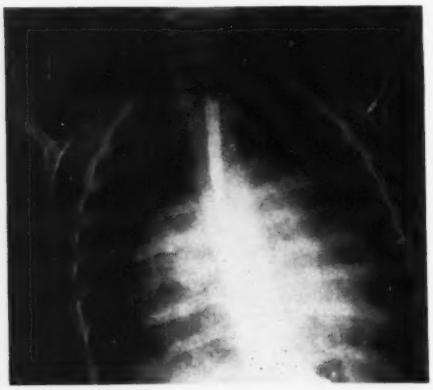


FIG. 4. Case 2. Teleoroentgenogram with barium swallow showing cardiac enlargement with extreme prominence of right atrium.

	Pressure (mm. Hg) S/D	Mean	O_2 Content Vol. %
Rt. Pulmonary Artery	65/30	42	11.05
Rt. Ventricle (outflow)	65/0	25	11.6
Rt. Atrium (mid)	—	±0	11.25
Superior vena cava	—	—	8.0
Capacity	—	—	15.2

These data suggested the presence of a left-to-right shunt into the right atrium and were interpreted as most probably the result of an atrial septal defect. The episode of atrial fibrillation was

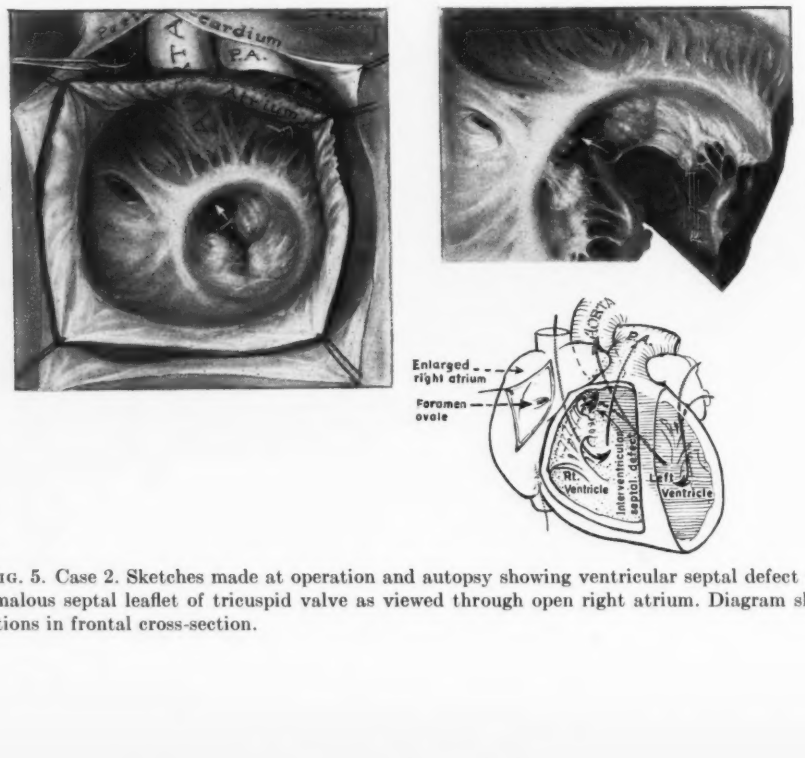


FIG. 5. Case 2. Sketches made at operation and autopsy showing ventricular septal defect with anomalous septal leaflet of tricuspid valve as viewed through open right atrium. Diagram shows relations in frontal cross-section.

treated with intramuscular quinidine and the mechanism reverted to a sinus one within 18 hours. The patient was discharged to return at a later date for surgical repair of his defect.

He was admitted for the third time on Jan. 5, 1954. He had been well between admissions and physical examination was essentially unchanged. The heart was greatly enlarged with a tremendous right atrium (fig. 4). He weighed 29¾ pounds and was 53 inches tall. Electrocardiogram and cardiac fluoroscopy were unchanged. The patient was digitalized preoperatively and on Jan. 8, 1954 operation was performed in the hope that an atrial septal defect might be closed. Anesthesia was induced with cyclopropane and hypothermia induced by immersing the patient in ice water until his body temperature had fallen to 28 C. A transverse anterior intercostal incision was placed in the fourth intercostal space with transection of the sternum. The heart was so large, the right atrium in particular, that it was necessary to divide the costal cartilages of the fifth, sixth and seventh ribs in order to expose the inferior vena cava. There was no evidence of any anomaly of venous return. Palpation through the enormous right atrium revealed a vigorous systolic thrill and a jet of blood was ejected into the right atrium with each systole. Both venae cavae were occluded with tapes. A Satinsky clamp occluded the pulmonary artery and aorta and the right atrium was opened widely. The atrial septum was intact. A jet of blood was seen regurgitating from the region of the tricuspid valve. Examination of this area revealed a 1 by 2 cm. defect which was interpreted by the surgeon as a patent ostium primum. The defect lay immediately below the annulus of the tricuspid ring and seemed to be in continuity with the tricuspid valve itself. Closure of the defect was carried out with continuous suture of 3-0 silk. After closing the defect the atrium was flooded with saline. Potts ductus clamps were applied to the atrial incision. The aortic clamps were removed and the superior vena cava was opened allowing blood to return to the heart. The total time of inflow stasis was 10 minutes. Heart action had been slow but regular during the period of open cardiotomy. Heart action continued to be feeble but regular for about one minute after the venae cavae had been opened, when ventricular fibrillation supervened. Prolonged cardiac massage, defibrillation with electric shocks and intracardiac potassium were used to no avail.

The significant postmortem findings were limited to the heart. The heart weighed 160 Gm. The right atrium was greatly enlarged and showed a recent surgical incision closed with silk. The great vessels appeared quite normal in position and appearance. The foramen ovale was patent at its anterior margin with a lumen of approximately 0.5 cm. by 1 cm. The right ventricle measured 5 mm. in thickness, as did the left. The tricuspid valve measured 8 cm. in circumference. There was a defect in the ventricular septum approximately 1 cm. by 2 cm. in size. Adjacent to this defect the septal leaflet of the tricuspid valve appeared deformed, being small, thickened and nodular (fig. 5). On the left side of the heart the interventricular septal defect presented in the aortic outflow tract high in the membranous portion of the left ventricular septum just beneath the aortic valve and between two adjacent commissures of the aortic cusps. On the right side the defect was associated with the septal leaflet of the tricuspid valve and presented just below the annulus of the valve. Several chordae tendineae of the valve leaflet were attached below the defect. There was a small amount of air in the coronary arteries.

Comment

These two cases illustrate an unusual type of abnormal communication between cardiac chambers. Whereas the usual type of defect in the membranous portion of the ventricular septum allows a shunt between the left ventricle and the right ventricle, in each of these patients the shunt through the interventricular septal defect was directed into the right atrium. Cardiac catheterization data in each case indicated the presence of a shunt of highly oxygenated blood entering the right atrium. Diagnostic considerations before operation included atrial septal defect, anomalous pulmonary veins draining into the right atrium and interventricular septal defect with tricuspid insufficiency and regurgitation of shunted blood back into the right atrium. Another anomaly which may result in a shunt of arterial blood into the right atrium is congenital aneurysm of a sinus of Valsalva of the aortic valve with erosion through the atrial wall and establishment of an aorticoatrial fistula.

In each of these cases the shunt was interpreted before operation as indicating an atrial septal defect. In retrospect there are several points which should have raised considerable question as to the correctness of this diagnosis. The presence of a loud, coarse systolic murmur accompanied by a readily palpable systolic thrill certainly indicated something other than uncomplicated atrial septal defect. Signs of tricuspid insufficiency were present in one case and in the other there was tremendous enlargement of the right atrium. Right ventricular and pulmonary arterial

hypertension was present to a considerable degree in both instances and in one patient approached systemic levels of pressure. This degree of right-sided hypertension is uncommonly encountered in atrial septal defects in young children. It would seem logical to suspect the presence of a left ventricular-right atrial shunt resulting from a high interventricular septal defect with a defective septal leaflet of the tricuspid valve in a patient presenting catheterization evidence of a shunt of highly oxygenated blood entering the right atrium and the clinical findings of a coarse systolic murmur and thrill over the midportion of the heart. The rare instances of aorticoatrial shunt resulting from rupture of an aneurysm of a sinus of Valsalva into the right atrium might be differentiated from this syndrome by the presence of a continuous murmur over the base of the heart in most patients with aorticoatrial shunts.

It was technically possible to close this form of ventricular septal defect through a right atrial approach in both of these cases, although the defective septal leaflet of the tricuspid valve was irreparable. Lack of understanding of the nature of the anomaly certainly did not facilitate its surgical handling in either instance. There have been several case reports of this type of ventricular defect, with minor modifications, which might lend themselves to surgical closure through a right atrial approach.[2, 3, 4, 5] These have been reviewed recently by Perry, Burchell and Edwards.[6]

The embryologic origin of such a congenital anomaly is of some interest. Anatomically, the membranous portion of the ventricular septum of the adult heart has a segment which lies between the floor of the right atrium and the aortic cone of the left ventricle. This is the socalled atrioventricular part of the membranous septum, which was formed from the right tubercles of the endocardial cushions of the atrioventricular canal and the conus septum.[7] An arrest in the development of this portion of the septum might give rise to this combination of atrioventricular communication with defective formation of the tricuspid valve.

Summary

Two unusual cases of a congenital communication between the left ventricle and the right atrium, with defective medial leaflet of the tricuspid valve, are reported. In both cases the diagnosis was misinterpreted as interatrial septal defect from data obtained at cardiac catheterization. In both cases, surgical closure was attempted with fatal results; postmortem studies revealed the true nature of the defect.

Summario in Interlingua

Es presentate duo simile casos de inusual anormalitates del corde. Existeva in illos un communication directe inter le ventriculo sinistre e le auriculo dextere via un defecto in le portion membranose del septo interventricular. Isto esseva associate con un formation defective del foliolo medial del valvula tricuspide. In ambe casos datos es presentate que esseva obtenite per catheterisation, durante le operation, e al autopsia. Es discutite le diagnose differential de iste typo de lesion.

REFERENCES

1. Helmsworth, J. A., Clark, L. C., Kaplan, S. and Sherman, R. T.: An oxygenator pump for use in total by-pass of heart and lungs. J. Thoracic. Surg. **26:** 617, 1953.
2. Buhl, quoted by Meyer, H.: Über Angeborene Enge oder Verschluss der Lungenarterienbahn. Virchows Arch. f. path. Anat. **12:** 497, 1857.
3. Gutzeit, K.: Ein Beitrag zur Frage der Herzmissbildungen an Hand eines Falles von kongenitaler Defektbildung im hautigen Ventrikelseptum und vom gleichzeitigem Defekt in dem diesem Septumdefekt anliegenden Klapperzipfel der Valvula Tricuspidalis Virchows Arch. f. path. Anat. **237:** 355, 1922.
4. Hemsath, F. A., Greenberg, M. and Shain, J. H.: Congenital cardiac anomalies in infants. Report of five cases. Am. J. Dis. Child. **51:** 1356, 1936.
5. McCullough, A. W. and Wilbur, E. L.: Defect of endocardial cushion development as a source of cardiac anomaly; A presentation of four cases from autopsy reports. Am. J. Path. **20:** 321, 1944.
6. Perry, E. L., Burchell, H. B. and Edwards, J. E.: Congenital communication between the left ventricle and the right atrium: Co-existing ventricular septal defect and double tricuspid orifice. Proc. Staff Meet., Mayo Clinic **24:** 198, 1949.
7. Gould, S.: Pathology of the Heart. Springfield, Charles C Thomas, 1953.

Cardioaortic Fistula

A Case Diagnosed in Life and Treated Surgically

By J. W. Brown, M.D., F.R.C.P., D. Heath, M.B., Ch.B. and W. Whitaker, M.D., B.Sc., M.R.C.P.

A case of cardioaortic fistula, due to rupture of an aneurysm of a sinus of Valsalva into the right ventricle, is described. This case was diagnosed in life and treated surgically one year later when the patient was admitted to hospital with bacterial endocarditis. The clinical features are discussed and the role of special methods of investigation in the diagnosis of the condition is defined. The importance of cardiac catheterization is stressed. The operative technique is described briefly. Following the patient's death from the uncontrolled infection an autopsy examination was carried out and the findings in the heart and small pulmonary vessels are given.

MANY EXAMPLES of congenital aortic sinus aneurysms have been described since this cardiac anomaly was first recorded by Thurnam[1]. Morgan Jones and Langley,[2] who described four cases and reviewed 23 others, considered that it was difficult to diagnose in life both the unruptured aneurysm and that which has given rise to a cardioaortic fistula and thought that it was almost certainly impossible to distinguish clinically a cardioaortic fistula from an aortopulmonary septal defect or even from a patent ductus arteriosus. They felt that the development of bacterial endocarditis in a patient with no previous evidence of heart disease should suggest the possibility of an underlying unruptured congenital sinus aneurysm. Falholt and Thomsen[3] have since shown that this lesion may be demonstrated in life by aortography. Venning[4] reported a case of cardioaortic fistula which had been recognised clinically but thought that the diagnosis was a matter of academic interest rather than of practical importance. However, recent advances in cardiac surgery have made treatment of a cardioaortic fistula a possibility. The purpose of this paper is to describe such a case diagnosed in life by cardiac catheterization and subsequently treated by surgery.

Case Report

A girl, aged 17 years, was admitted in January, 1953, a pyrexia emergency. At the age of 9, a cardiac murmur was found during a routine school medical inspection. She was referred to one of us (J. W. B.) and on the basis of a continuous left parasternal murmur was diagnosed as a case of patent ductus arteriosus. At that time her general health was excellent, she was not breathless on exertion, had no cough and she continued symptom free until two weeks before admission when she began to feel weak and shivery and complained of aching in her muscles. On admission she was pale and febrile (103 F.) and blood culture grew a streptococcus viridans sensitive to penicillin. She was treated by injection of 2 million units of penicillin daily for six weeks. After seven days she was apyrexial and recovered without incident.

After treatment, the underlying cardiac lesion was investigated. On clinical examination the radial pulse was regular at 100 per minute and was collapsing. The blood pressure in the arms was 140/0 mm. Hg. Both femoral pulses were palpable. The jugular venous pressure was not raised. The apex beat was palpable in the fifth left intercostal space four inches to the left of the midline and the character of the cardiac impulse suggested left ventricular hypertrophy. There was no clinical evidence of pulmonary hypertension. On auscultation there was a loud precordial systolic murmur of maximum intensity in the fourth left intercostal space in the parasternal line, which was widely conducted throughout the chest and an early high-pitched diastolic murmur maximum in the fourth left intercostal space. At times the murmur appeared to be continuous in the fourth left intercostal space.

The electrocardiogram indicated left ventricular hypertrophy (fig. 1). Teleradiographic examination was normal but on screening there was evidence of slight left ventricular hypertrophy (fig. 2). There was increased pulsation of the main pulmonary artery but no expansile pulsation was seen in the peripheral branches. Angiocardiography showed faint but definite reopacification of the pulmonary arteries at seven seconds and the contrast medium remained

From The Regional Cardiovascular Centre, City General Hospital and The University Department of Medicine, Royal Hospital, Sheffield, England.

in the pulmonary arteries for an abnormally long time. The hemoglobin was 10.5 Gm. per 100 ml. The results of cardiac catheterization are shown in table 1.

From these it was concluded that there was a left-to-right shunt of blood into the right ventricle and in view of the low systemic diastolic pressure, it was presumed that this was from the aorta rather than from the left ventricle. A diagnosis of a congenital aneurysm of a sinus of Valsalva which had ruptured into the right ventricle appeared to be in agreement with all the findings of clinical and special investigation. In view of the risk of reinfection, surgical repair was advised but the patient's mother decided against this.

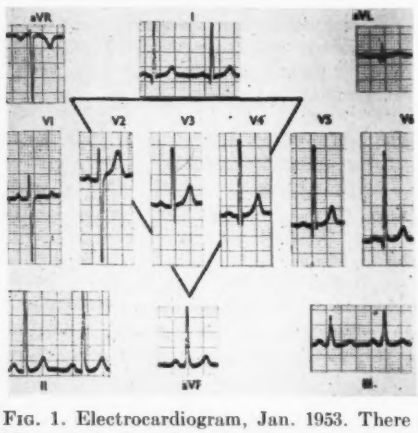


FIG. 1. Electrocardiogram, Jan. 1953. There are tall R waves in the left ventricular surface leads and deep S waves in the right ventricular surface leads which are indirect evidence of left ventricular hypertrophy.

After discharge in March, 1953 the patient remained in good health until August, 1954 when she was readmitted with a second attack of endocarditis. Shortly before admission she developed a boil on the left side of her face and this was probably the source of her infection as on this occasion the infecting organism proved to be a coagulase positive *Staphylococcus aureus*.

The cardiac signs were the same as on her previous admission, except that cardiac enlargement had occurred, the apex beat being in the sixth left intercostal space in the anterior axillary line. The cardiac enlargement was confirmed by radiological examination (fig. 2). As the staphylococcus was resistant to penicillin in vitro, the infection was treated initially by streptomycin and later, when there was no response, by aureomycin and erythromycin. After one month, when it was evident that the infection was uncontrolled by the antibiotic therapy, the only hope of cure lay in repairing the fistula and the patient was transferred to Professor P. R. Allison at Leeds General Infirmary for surgical treatment on September 27. Four days after admission to the surgical wards temperatures of 103 F. and 104 F. were recorded although she was still receiving erythromycin. The white cell count had risen from 8,700 on admission to 20,000 per cu.mm. Three days later the pulse became irregular and the electrocardiogram showed dissociation between the auricles and ventricles, the nodal rate slightly exceeding the sinus rate. Blood cultures still grew a *Staphylococcus aureus*, insensitive to peni-

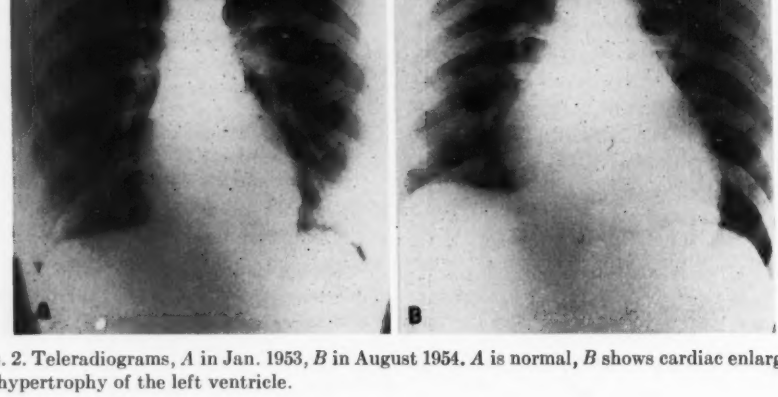


FIG. 2. Teleradiograms, *A* in Jan. 1953, *B* in August 1954. *A* is normal, *B* shows cardiac enlargement with hypertrophy of the left ventricle.

cillin and streptomycin but sensitive to aureomycin, terramycin and erythromycin in vitro. After transfusion with three pints of blood the patient was explored under hypothermia on Oct. 5, 1954. Blanket cooling was used, assisted by Largactil, Phenergan and Pethidine under general anesthesia. The cooling process was slow, presumably due to her pyrexia, and after three hours the operation was started, when her temperature was 84 F.

The sternum was split from end to end. A strip of pericardium was resected, doubled on itself and sutured into a button in case it was needed for closing the defect. The right ventricle was greatly enlarged and there was a marked expansile pulsation of the conus in diastole. There was a continuous thrill low down in the ventricle but nothing abnormal could be felt in the main vessels. There was no dilatation of the aorta or pulmonary artery. The two venae cavae were isolated and string passed round them for occlusion when necessary. The pulmonary artery was then separated from the aorta and a string passed around it. A clamp was applied to the aorta ready for closure. The vessels were occluded in the following order: venae cavae, pulmonary veins, pulmonary artery and aorta. A long incision was then made in the right ventricle between two rows of holding sutures previously inserted. The pulmonary valves and the conus appeared normal. There was a hole about 1 cm. in diameter partly overshadowed by the uppermost *chordae tendinae* of the tricuspid valve and in fact not very far away from the upper part of the valve itself. A large vegetation was flapping from it. The heart was thoroughly washed out with a few pints of saline and the vegetation removed. The hole was then closed by means of a mattress suture of braided wire on an atraumatic intestinal needle and reinforced by a single wire suture alongside it. The occlusion seemed to be complete. Sutures of catgut on atraumatic intestinal needles were then passed through the ventricular wall, very frequent flushings with saline being used to try to get air out of the heart. As soon as the sutures had been inserted, the strings were released in the same order in which they had been applied. The heart was dilated and inert with very slight fibrillation. Cardiac massage was applied immediately and adrenaline injected into the left ventricle. Very little tone returned and defibrillation was tried without success. A clamp was applied to the aorta, further adrenaline injected into the left ventricle and massage applied to get adrenaline into the coronary arteries. Such measures as these, combined with frequent defibrillation, were carried out until finally some normal but weak beats occurred. At this stage, calcium chloride was injected and massage continued until a strong beat developed. Of all the measures used, defibrillation seemed more effective than anything else, particularly when the electrodes were fairly wide part. Some further sutures were inserted in the wall of the venae cavae and the chest closed with drainage of the mediastinum and pleural cavities. During the operation the circulation was occluded for seven and one half minutes when the patient's temperature was 29 C. Spontaneous and effective beats were produced 35 minutes after releasing the clamps.

TABLE 1.—*Results of Cardiac Catheterization*

Site	Blood Oxygen Saturation, Per Cent	Blood Pressure in mm. Hg
Femoral artery	99.5	140/0
Left pulmonary artery	91.5	—
Right pulmonary artery	93.6	12 (mean)
Main pulmonary artery	92.4	—
High right ventricle	91.0	9 (mean)
Low right ventricle	93.1	—
Low right atrium	78.0	−2 (mean)
High right atrium	83.8	—
Superior vena cava	75.0	—

During the postoperative period the patient remained comatose but reacted to pain. On the fourth day she spoke to her parents and then relapsed into a semicoma again. Throughout this period her systolic blood pressure was 130 but the diastolic pressure was zero. Erythromycin and Terramycin were given throughout and on the fourth day gastroscopy was performed for feeding purposes. However, the infection was uncontrolled and she died on the fourteenth postoperative day with multiple visceral staphylococcal abscesses.

Autopsy Report

The heart was enlarged, mainly due to hypertrophy of the right ventricle, and weighed 400 Gm. The right and posterior (noncoronary) sinuses of Valsalva had undergone aneurysmal enlargement, especially the former (figs. 3 and 4). The left sinus of Valsalva was normal. The aneurysm of the right sinus continued as a fistula 33 mm. long to open into the right ventricle just anterior to the anterior cusp of the tricuspid valve on the crista supraventricularis. The aortic valve was incompetent due to partial detachment of the right coronary cusp. The tricuspid and mitral valves were normal, admitting three and two fingertips, respectively. The pulmonary valve was normal. The pulmonary artery arose normally from the right ventricle, was not dilated and was free of atheroma. There were no septal defects. The aorta was free from atheroma. The thickness of the ventricular walls in the region of the apex was 1 cm. in the case of the right ventricle and 1.5 cm. in the case of the left. There were multiple septic infarcts of both lungs and the spleen but not in the other organs, including the brain, kidneys and liver. Swabs from the vegetations on the aortic valve grew *Staphylococcus aureus.*

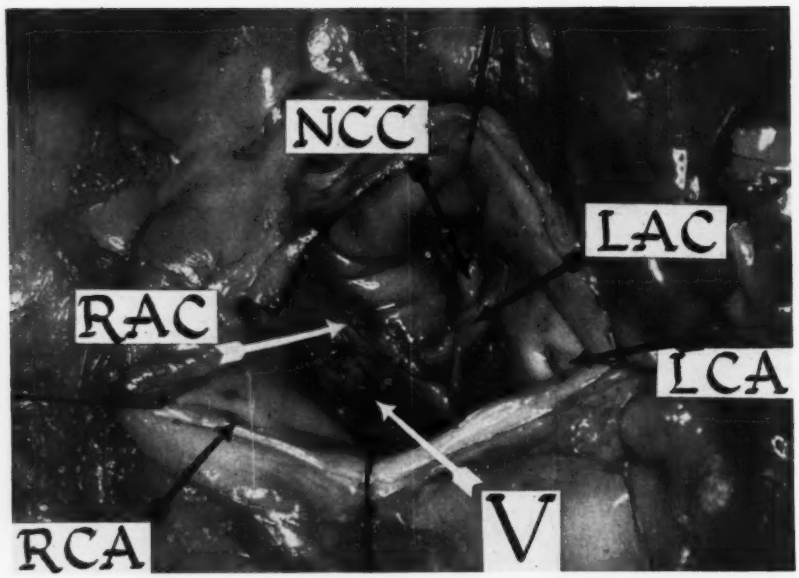


FIG. 3. View of the sinuses of Valsalva from the aorta. The right, left and noncoronary cusps and the origins of the right and left coronary arteries are shown. The right sinus of Valsalva has undergone aneurysmal enlargement and is covered with vegetations. LCA = Left coronary artery. RCA = Right coronary artery. LAC = Left aortic cusp. RAC = Right aortic cusp. NCC = Noncoronary cusp. V = Vegetations.

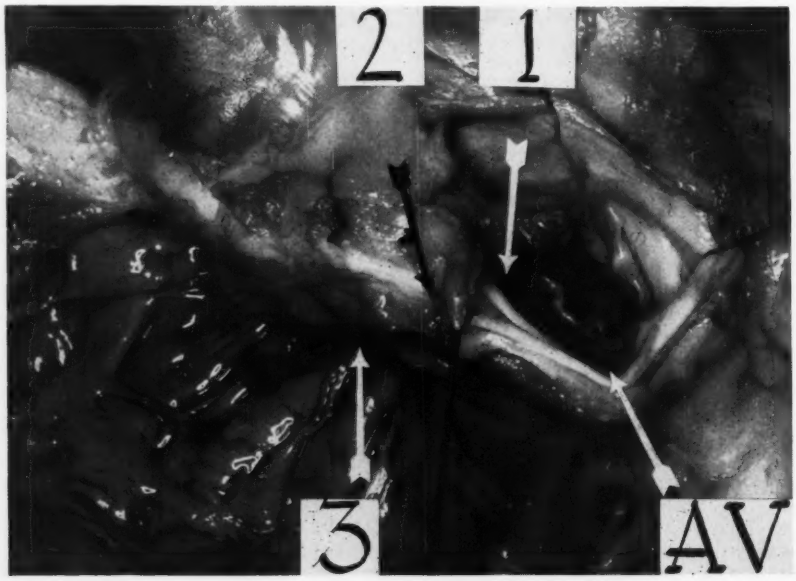


FIG. 4. View of the course of the cardioaortic fistula. The fistula opens from the right sinus of valsalva (1) passes through the wall of the right ventricle (2) and opens into the sinus of the right ventricle (3). A matchstick has been passed through the fistula from the aorta to the right ventricle. AV = Aortic valve.

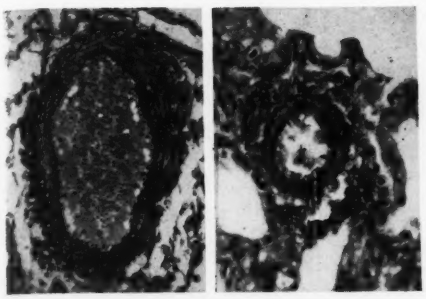


FIG. 5. Two pulmonary vessels stained by Verhoeff/Van Gieson stain to demonstrate muscle, elastic and fibrous tissue. The vessel on the right is an abnormal pulmonary arteriole with a distinct media lying between thick elastic membranes. There is slight intimal proliferation of fibrous tissue. These changes indicate pulmonary hypertension. The vessel on the left is a muscular pulmonary artery. There is no intimal proliferation of fibrous tissue and the thickness of the media is within normal limits.

The Pulmonary Vessels. The elastic pulmonary arteries (>1000 μ in diameter) had no atheromatous deposits on the intima and there was no medial necrosis.

The muscular pulmonary arteries (100 to 1000 μ in diameter) were normal in appearance (fig. 5). The thickness of the media was 10 per cent of the external diameter of the vessel and there was no subintimal proliferation of fibrous tissue. The adventitia was normal. The elastic membranes were thick.

The pulmonary arterioles (<100 μ in diameter) were abnormal (fig. 5). This type of vessel normally has no media but consists solely of a single elastic membrane lying between intima and adventitia. In this case, however, all the arterioles were characterised by a thick media lying between thick elastic membranes and this abnormal media was present in arterioles with as small a diameter as 30 μ.

The veins and venules were normal. There was no thrombosis in any type of pulmonary vessel.

DISCUSSON

Symptomatology

Morgan Jones and Langley[2] thought that patients with unruptured congenital aortic sinus aneurysms were characteristically free from symptoms until they developed subacute bacterial endocarditis. Such was the history of this patient. When investigated after treatment of her first attack of subacute bacterial endocarditis, she was found to have a cardioaortic fistula. It is impossible to say whether the fistula in this case had developed as a complication of the infection or was congenital in origin. The absence of any dramatic incident suggests that the fistula was congenital in origin rather than an acquired lesion. Rupture of hitherto silent aneurysms described by Eppinger[5] and Venning[4] has been characterized by sudden intense breathlessness associated with severe chest pain and vomiting. However, the aneurysm may have ruptured during the first attack of endocarditis without the dramatic symptoms usually associated with this event and this is supported by the fact that the heart was of normal size at this time and then enlarged rapidly in the following year (fig. 2). The continuous murmur which was noted at the age of 9 years is of no diagnostic value since such murmurs have been noted in the unruptured congenital aortic sinus aneurysms[3] as well as in patients with a cardioaortic fistula.

Signs

A high pulse pressure, a murmur, which is at times continuous and at other times "to and fro" in character and of maximum intensity in the fourth left intercostal space, cardiac enlargement and a cardiac impulse suggestive of left ventricular hypertrophy, as were observed in this case, are classical signs of a cardioaortic fistula. Edwards and co-workers[6] described a continuous murmur maximum in the second left intercostal space in a case with a systemic blood pressure of 180/0–60 mm. Hg where a congenital aortic sinus aneurysm had ruptured into the right ventricle. Herson and Symons[7] and Venning[4] also noted continuous murmurs and high pulse pressures in patients with cardioaortic fistula opening into the right auricle but Hirschboek[8] and Macleod[9] observed only systolic and diastolic murmurs in the region of the sternum in such patients. It is interesting to note that in the present patient the murmurs were at times to-and-fro and at other times continuous in character. The continuous murmur in cardioaortic fistula may be due to the passage of blood through the fistula from the aorta throughout the cardiac cycle but Falholt and Thomsen[3] noted that such murmurs have been described with unruptured aneurysms and thought that these were due to the rush of blood in and out

of the aorta in systole and diastole. Although the signs observed in the present case are characteristic of a cardioaortic fistula they are not pathognomonic of one since identical signs occur in the much commoner anomalies of patent ductus arteriosus and aortopulmonary septal defect where a left-to-right shunt occurs distal to the aortic valve and in patients with aortic stenosis and incompetence. It may be impossible to distinguish clinically a cardioaortic fistula from these conditions.

Electrocardiography

The electrocardiogram in the present patient indicated left ventricular hypertrophy (fig. 1). In general, electrocardiograms provide little positive evidence in the diagnosis of the anomaly under discussion. In seven of the patients described or reviewed by Morgan Jones and Langley[2] where electrocardiograms were available there was left axis deviation in three, right axis deviation in two, auricular fibrillation in one and heart block in one. Venning's[4] first case showed right bundle branch block, first degree heart block and widened bifid P waves, the second a digitalis effect only, the third left bundle branch block and the fifth the Q_3T_3 pattern of infarction. The electrocardiogram in the case of Edwards and associates[6] showed sinus rhythm and left ventricular hypertrophy.

Radiological Examination

In the seven cases of cardioaortic fistula reviewed by Morgan Jones and Langley[2] there was enlargement of both ventricles on radiologic examination but no localized swellings were noted to indicate an aneurysm although Roesler[10] and Ostrum and his colleagues[11] have described small projections from the vascular pedicle in patients with unruptured aneurysms. Morgan Jones and Langley[2] made no comment on the pulmonary arterial pulsations but Edwards and colleagues[6] noted increased pulsation of the pulmonary arteries in their case and Venning[4] also found expansile pulsation of the small branches of the pulmonary artery which he considered as marked as in patients with auricular septal defects. This latter author regarded radioscopy of diagnostic importance in cardioaortic fistula but this was not so in the present case where there was no expansile pulsation in the peripheral branches of the pulmonary artery and where the increased pulsation of the main pulmonary arteries and the left ventricular hypertrophy were not pathognomonic of the anomaly.

Angiocardiography

On angiocardiographic examination there was slight reopacification of the pulmonary arteries seven seconds after the injection. The contrast medium must have re-entered the right ventricle from the aorta via the cardioaortic fistula to produce this reopacification but there was no conclusive evidence of this flow and such reopacification as was seen in the pulmonary arteries could theoretically have occurred from an aortopulmonary septal defect or from a patent ductus arteriosus. Unruptured congenital aortic sinus aneurysms have been demonstrated by aortography[3] and with venous angiocardiography by the present authors.

Cardiac Catheterization

As would be expected, Falholt and Thomsen[3] found nothing abnormal at cardiac catheterization in a patient with an unruptured sinus aneurysm and without any evidence, they believed, that this investigation would be of no assistance in differentiating a ruptured aneurysm from a patent ductus arteriosus or an aortopulmonary septal defect unless the ductus or septal defect were actually catheterized. However, Edwards and co-workers[6] catheterized a patient in whom an aneurysm had ruptured into the right ventricle and found a blood oxygen saturation of 78 per cent in the right ventricular inflow tract and 94 per cent in the right ventricular outflow tract which they considered of diagnostic importance, indicating that blood of high oxygen saturation was shunting into the right ventricle. Since the blood pressure in the arms in this patient was 180/0 mm. Hg, cardioaortic fistula was diagnosed. In the case now reported, the diagnosis was based on similar findings. The results of cardiac catheterization (table 1) indicated a shunt of blood of high oxygen saturation into the right ventricle and there was also a high systemic pulse pressure. In contrast to the case of Edwards and associates[6] in

whom the left pulmonary-artery blood pressure was 60/23 the pulmonary-artery blood pressure was normal when recorded following her first attack of endocarditis a year before death.

Histology of Pulmonary Vessels

The hemodynamic changes with this anomaly are similar to those occurring with patent ductus arteriosus. The pulmonary-artery blood pressure in the present case was normal one year before death and, since Heath and Whitaker[12] found that the pulmonary arterioles were normal in eight patients with patent ductus arteriosus with pulmonary artery mean blood pressures of 33 mm. Hg or less, it is believed that the pulmonary arterioles in this case would have been normal with no media if they had been examined at this time. However, after death they were abnormal, with a thick media and thick elastic membranes suggesting that the patient had developed pulmonary hypertension in the year following cardiac catheterization (fig. 5). If the cardioaortic fistula formed during the first attack of bacterial endocarditis, the resultant hemodynamic changes could account for the subsequent development of pulmonary hypertension and the rapid enlargement of the left ventricle.

Summary

A description is given of a patient with cardioaortic fistula which was diagnosed in life and treated surgically.

The patient was asymptomatic until an attack of subacute bacterial endocarditis at the age of 17 and evidence is presented which suggests that the cardioaortic fistula developed from the rupture of a congenital aortic sinus aneurysm at this time. On clinical examination after the first attack of endocarditis there was a high pulse pressure, a murmur which was at times continuous and at times "to and fro" in character, of maximum intensity in the fourth left intercostal space, and a cardiac impulse suggestive of left ventricular hypertrophy. In the absence of a classical history of rupture of a congenital aneurysm into the right ventricle or auricle the history and examination did not provide the diagnosis which could equally well have been one of patent ductus arteriosus, aortopulmonary septal defect or aortic stenosis with incompetence.

Electrocardiography and teleradiography were normal. Angiocardiography revealed faint but definite reopacification of the pulmonary arteries. Cardiac catheterization demonstrated a shunt of oxygenated blood into the right ventricle and established the diagnosis.

A second attack of endocarditis occurred a year after the first. In the intervening period cardiac enlargement had occurred. Since the staphylococcus causing the second infection was resistant to antibiotic therapy, an attempt was made to treat the infection surgically. The operative technic for repair of the fistula is described briefly. The patient died 14 days postoperatively from an uncontrolled staphylococcal pyemia. Autopsy findings in the heart and small pulmonary vessels are given.

Acknowledgments

We wish to thank Professor P. R. Allison and his staff at the Department of Thoracic Surgery, Leeds General Infirmary, who performed the operation. We also wish to thank Miss E. K. Abbott, Consultant Radiologist, City General Hospital, for radiologic facilities and Mr. C. Lambourne for technical assistance.

Summario in Interlingua

Es describite le caso de un patiente con fistula cardioaortic que esseva diagnosticate in vivo e tractate chirurgicamente.

Le patiente esseva sin symptomas usque al etate de 17 annos quando ille habeva un attacco de subacute endocarditis bacterial. Nostre observationes suggere que le fistula cardioaortic resultava a ille tempore ab le ruptura de un congenite aneurysma del sinus aortic. Post le prime attacco de endocarditis le examine clinic revelava (1) un alte pression del pulso, (2) un murmure que esseva a vices continue e a altere vices de character fluctuante, con un intensitate maximal in le quarte spatio intercostal sinistre, e (3) un impulso cardiac que pareva indicar hypertrophia sinistroventricular. Proque le caso non sequeva le historia classic de rupturas de aneurysmas congenite a in le ventriculo o auriculo dextere, le diagnose non poteva esser establite super le base del examine o del historia del patiente. Istos esseva equal-

mente indicative de o patente ducto arteriose o defecto del septo aortopulmonar o stenosis aortic con incompetentia.

Le constationes electrocardiographic e teleradiographic esseva normal. Le examine angiocardiographic revelava un leve sed distincte re-opacification del arterias pulmonar. Catheterisation cardiac demonstrava un derivation de sanguine oxygenate a in le ventriculo. Isto establiva le diagnose.

Un secunde attacco de endocarditis occurreva un anno post le prime. Durante le intervallo allargamento cardiac habeva occurrite. Proque le staphylococco que causava le secunde infection se monstrava resistente al therapia antibiotic, un tractamento chirurgic esseva tentate. Nos describe brevemente le technica operative que esseva usate in reparar le fistula.

Le patiente moriva 14 dies post le operation in consequentia de un non-controlabile pyemia staphylococcal. Es presentate constatationes autoptic in le corde e le parve vasos pulmonar.

REFERENCES

[1] THURNAM, J.: On aneurysms and especially spontaneous varicose aneurysms of the ascending aorta and sinuses of Valsalva. Med-Chir. Trans. **23:** 323, 1840.

[2] MORGAN JONES, A. AND LANGLEY, F. A.: Aortic sinus aneurysms. Brit. Heart J., **11:** 325, 1949.

[3] FALHOLT, W. AND THOMSEN, G.: Congenital aneurysm of the right sinus of Valsalva, diagnosed by Aortography. Circulation **8:** 549, 1953.

[4] VENNING, B. M.: Aneurysms of the Sinuses of Valsalva. Am. Heart J. **42:** 57, 1951.

[5] EPPINGER, H.: Zur Diagnostik eines wahren Aneurysma des Sinus Valsalvae dexter. Wien med. Wschr. **66:** 65, 1916.

[6] EDWARDS, J. E., DRY, T. J., PARKER, R. P., BURCHELL, H. B., WOOD, E. H., AND BULBULIAN, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels. Springfield, Charles C Thomas, 1954.

[7] HERSON, R. N. AND SYMONS, M.: Ruptured congenital aneurysm of the posterior sinus of Valsalva. Brit. Heart J. **8:** 125, 1946.

[8] HERSCHBOECK, F. J.: Aneurysm of one of the sinuses of Valsalva caused by a congenital lesion. Am. Heart J. **24:** 550, 1942.

[9] MACLEOD, A.: Cardioaortic Fistula. Brit. Heart J. **6:** 194, 1944.

[10] ROESLER, H.: Clinical Roentgenology of the Cardiovascular System, Baltimore, pp. 327, 407, 1943.

[11] OSTRUM, H. W., ROBINSON, B. D., NICHOLS, C. F. AND WIDMAN, B. P.: Aneurysms of aortic sinuses or sinus of Valsalva. Am. J. Roentgenol. **40:** 828, 1938.

[12] HEATH, D. AND WHITAKER, W.: The pulmonary vessels in patent ductus arteriosus. J. Path. and Bact. In press.

The Physiologic and Clinical Similarity Between Primary Amyloid of the Heart and Constrictive Pericarditis

By ROLF M. GUNNAR, M.D., ROBERT F. DILLON, M.D., RICHARD J. WALLYN, M.D. AND EDWARD I. ELISBERG, M.D.

When primary amyloid infiltrates the myocardium, there is a loss of distensibility and a resistance to contraction similar to that seen in constrictive pericarditis. The clinical similarity between these two entities has been noted previously on only a few occasions and only one previous case of amyloid has had catheterization studies. A case of amyloid of the heart is presented with catheterization studies and the reasons for the clinical and physiologic similarity to constrictive pericarditis are discussed.

THE essential pathology of constrictive pericarditis is the partial replacement of the epicardium and superficial myocardial layers by inelastic fibrous tissue. This interferes with diastolic filling of the ventricles and is recorded during right ventricular catheterization as a high end-diastolic plateau. In addition, the encasing and infiltrating lesion interferes with contractility and thereby reduces, somewhat, the systolic pressure anticipated in relation to the high diastolic filling pressure. This results in a pressure pattern in which the end-diastolic pressure is often greater than one-third the systolic pressure: a finding which has been considered diagnostic by some authors.[1] The early diastolic dip seen in the right ventricular curve is due to the "drag" effect of the fibrous exterior and its tendency to resist change and to reach the resting state more quickly. It is fairly sharply demarcated because of rapid filling caused by the high pressure within the auricle.

Recently it has been shown by Hertzel, Wood and Burchell[2] that similar pressure patterns can be found in other conditions and in amyloid of the heart specifically. In 1950, Fisher[3] had shown the inability of the amyloid heart to augment its diastolic volume. Clinically this was not a new concept, for Couter and Reichert[4] and Findley and Adams[5] had noted the clinical similarity in patients with amyloid infiltration of the heart and those with constrictive pericarditis. Though a direct comparison of the two conditions had not been made prior to these reports, many cases of amyloid of the heart, as reported, demonstrated high venous pressure, low pulse pressure, marked peripheral edema, nonspecific electrocardiographic changes and unresponsiveness to conventional cardiac therapy as occurs in constrictive pericarditis.[6, 7, 8]

When amyloid infiltrates the myocardium, it would seem logical to assume that the same physiologic situations as seen in constrictive pericarditis occurs. The main difference would be that the constrictive element would now lie within the myocardium and hence, perhaps, interfere even more with the ejection force of the ventricle.

We have recently observed a case of "primary" amyloidosis with cardiac involvement that clinically and by catheterization studv simulated constrictive pericarditis.

CASE REPORT

E. R., a 49 year-old Negro woman, was admitted to Cook County Hospital Aug. 26, 1953, complaining of dyspnea, cough, ankle edema and abdominal pain. She had been well until November 1952, when she had an episode of right upper quadrant pain associated with some nausea and vomiting. This lasted about eight hours and a diagnosis of liver disease was made by her physician. She did fairly well until March 1953, when she began noticing swelling of the ankles and abdomen. The

From the Department of Medicine and the Hektoen Institute for Medical Research of The Cook County Hospital, Chicago, Ill.

ankle edema subsided with mercurials, but in July 1953 it recurred with increasing abdominal distention. At this time, the patient again had some "cramping" right upper quadrant pain. The edema persisted throughout the month prior to admission, despite mercurials. The patient developed a persistent, nonproductive cough a few days before admission and this was associated with exertional dyspnea. She denied orthopnea and paroxysmal nocturnal dyspnea, but at the time of admission seemed more comfortable while sitting up.

Her past history was negative for rheumatic fever, scarlet fever, heart disease and venereal disease. The patient had a very poor dietary history including no meat and very little bread. Systemic review revealed no sweats, fever, urinary difficulty or gastrointestinal complaints other than the right upper quadrant pain.

Physical examination revealed a chronically ill Negro woman, sitting up in bed in no acute distress. Blood pressure was 118/90, pulse 100, temperature 98 F., respiration 20 per minute. Her skin was dry. Pupils reacted to light and accommodation. The fundi were normal. The tongue was thought to be slightly larger than normal and somewhat reddened, but the patient stated it had been that way all her life. The neck veins were distended and pulsating. Examination of the chest showed flatness in the left base with decreased breath sounds. There were a few moist rales in both lung bases. The heart was enlarged to the anterior axillary line. The aortic second sound was equal to the pulmonic. The mitral first tone was accentuated and there was a protodiastolic gallop with a late diastolic rumble lasting up to the first tone. There was soft blowing apical systolic murmur. The liver was enlarged four finger-breadths below the costal margin with a firm, sharp edge. There was shifting flank dullness. Pitting edema extended over the thighs and abdominal wall. Pretibial edema was of moderate severity. Pelvic and rectal examinations were normal. The reflexes were physiological.

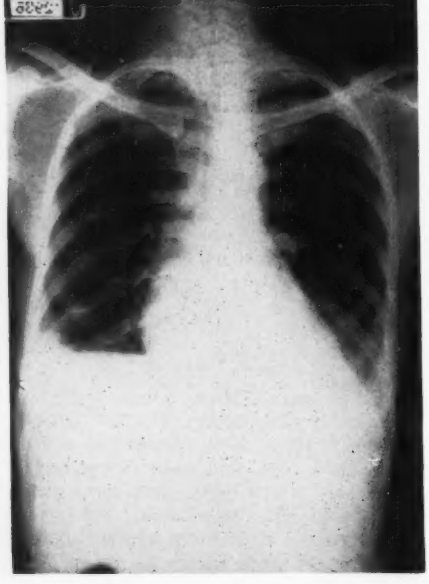


FIG. 1. Posteroanterior view of the chest after thoracentesis.

On August 29, a thoracentesis yielded 1300 cc. of slightly cloudy, straw colored fluid from the left pleural cavity. Following this the patient was able to lie flat in bed comfortably. Specific gravity of the fluid was 1.013.

Laboratory Findings: Urine: Specific gravity was 1.010, albumin 2 plus, sugar absent, and microscopic examination negative. Blood count: hemoglobin was 80 per cent, white blood cells 7,700 with 60 neutrophils, 7 band forms, 2 basophils, 28 lymphocytes and 3 monocytes. The sedimentation rate was 30 mm. in 1 hour. Kahn was negative. Smears and cultures of the pleural fluid were negative. Three blood cultures were negative. Non protein nitrogen was 41 mg. per/100 cc., total protein 7.4 Gm. per 100 cc., the albumin globulin ration 4.1:3.3, cholesterol 164 mg. per 100 cc., alkaline phosphatase 4.3 B. U., icterus index 6 units, gamma globulin 2.61 Gm. per 100 cc., thymol turbidity 2.0 units and cephalin flocculation 2 plus.

Chest x-ray films on admission showed a left pleural effusion. After thoracentesis other x-ray films showed a small amount of fluid in the right base. The heart appeared only slightly larger than normal with no characteristic configuration (fig. 1). Fluoroscopic examination of the heart revealed left atrial (fig. 2) and left ventricular enlargement with very poor pulsations, particularly of the left ventricle. Electrocardiograms showed low voltage in all leads with inverted T waves in V_3 through V_6 and aV_L, and flat T waves in aV_F.

Hospital Course: The patient was placed on a low-salt diet and given mercurial diuretics and digitalis with very little response. Single daily temperatures were consistently normal. On September 1, another left thoracentesis yielded 900 cc. of straw colored fluid with specific gravity of 1.013. The patient maintained a gallop rhythm and the edema. A Mantoux was positive 1:10,000. On September 9, venous pressure was 320 mm. of saline, and circulation time (magnesium sulfate) 27 seconds. On Sept. 11, 1953, the patient was started on streptomycin and para-aminosalicylic acid (PAS) because of the possibility of a tuberculous pericarditis. On Sept. 23, 1953, the chlorides were 83 mEq per liter, sodium 129 mEq per liter and potassium 3.2 mEq per liter and the patient was put back on a general diet. In addition she was given oral potassium chloride. The pleural fluid recurred

on the left and appeared on the right. Cardiac findings remained unchanged. About this time a purpuric skin lesion appeared on the anterior chest and neck which was considered to be a drug eruption by the dermatology consultants. The para-aminosalicylic acid was stopped and the patient was put on isoniazid.

By October 5, the nonprotein was 82 mg. per 100 cc., creatinine 3.4 mg. per 100 cc., chloride 98 mEq per liter, sodium 129 mEq. per liter, potassium 3.8 mEq. per liter. Because of lethargy, weakness and slight mental confusion the patient was given 300 cc. of 3 per cent saline intravenously with potassium chloride and oral fluids were restricted. The next day she was slightly improved but very weak. Blood pressure was 90/80, pulse 80. There was an increase in the purpuric skin lesion but the edema was unchanged. She was given an additional 300 cc. of 3 per cent saline and potassium chloride intravenously but expired early in the morning October 10, her fortyfifth hospital day.

Cardiac catheterization studies done on October 2 are shown in table 1 and figures 3 through 6 and will be discussed in relation to the postmortem findings.

Autopsy Findings: A specimen of skin was normal but unfortunately was not removed from the area of the purpuric lesion. The right pleural space contained 1500 cc. and the left 750 cc. of a clear, straw-colored fluid. The lungs were slightly edematous with some thickening of the hyperemic septa. The small branches of the pulmonary arteries revealed some intimal thickening.

The heart weighed 500 Gm. and the pericardial sac contained 10 cc. of a clear fluid. Both ventricles were enlarged but there was slight preponderance of the right ventricle. The epicardium appeared somewhat puckered but otherwise was free. Around the inferior vena cava at its entrance into the right atrium there were some fibrotic strands between the epi- and pericardium and extending slightly into the surrounding mediastinum. These adhesions caused slight kinking of the inferior vena cava which showed phlebosclerosis, but obviously were not contributory to the clinical picture since no similar obstruction to the inflow of the superior vena cava could be found. On section, these strands were apparently due to amyloid involvement of the pericardium. The myocardium of the right ventricles was thickened and the papillary muscles were flattened. The tricuspid valve was thickened irregularly but showed no anatomical evidence of dysfunction. The right atrium was dilated and thickened. The left atrium was dilated but its endocardium showed no thickening. The left ventricle was thick-walled and the papillary muscles were prominent. The mitral ring measured 8 cm. in diameter and the cusps were irregularly thickened throughout. The chordae tendinae were matted together and thickened. There was evidence of

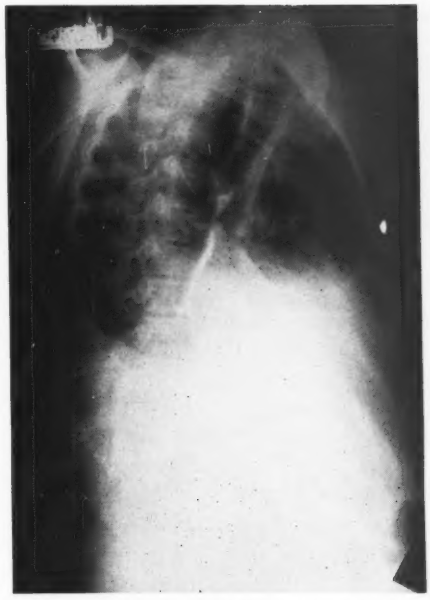


FIG. 2. Right anterior oblique view of the chest showing the barium filled esophagus displaced by the enlarged left atrium.

mitral stenosis and incompetence. Microscopic sections of the myocardium showed perivascular infiltration by a homogenous material which separated the muscle fibers. This did not stain with Congo red but stained metachromatic with methyl violet and was therefore atypical amyloid or paraamyloid. The deformity of the mitral valve was seen to be due to infiltration by a similar material.

The liver weighed 1800 Gm. and revealed severe passive congestion. The arteries showed extensive amyloid infiltration. The areas showing most marked amyloid showed more marked congestive changes. The spleen weighed 200 Gm. and showed marked amyloidosis of the arteries.

There was extensive amyloid infiltration of the skeletal muscles but not of the adrenals. The ovaries and thyroid showed amyloid infiltration. The kidneys showed lamellated casts especially in the distal convoluted tubules. These stained with congo red and a similar material could be seen in the glomerular spaces. There was a cellular reaction around the casts and in some places epithelial giant cells were seen. This was considered to be a myeloma kidney.

Microscopic sections of the bone marrow showed accumulations of immature plasma cells which in many areas replaced the normal bone marrow elements. Lymph nodes also showed tumor like groups of typical myeloma cells.

The final anatomic diagnosis was diffuse myelo-

matosis; primary amyloidosis with involvement of liver, spleen, muscle and the myocardium and mitral valve (resulting in some degree of mitral stenosis and incompetence); myelomatous nephropathy; and cardiac failure.

Comment

Clinically observed venous engorgement was confirmed by the finding of marked right atrial hypertension (fig. 3). The atrial tracing shows a rounded elevation coincident with ventricular activity and lending somewhat of an "M" or "W" shaped configuration to the over-all contour. The principle negative deviation of the atrial pressure curve occurs prematurely in the isometric relaxation phase of the ventricle and is due to the rapid egress of blood from atrium to ventricle when the intraventricular pressure falls below the venous pressure.

The ventricular pressure curves obtained (fig. 4) in the presence of an extensive amyloid deposition is one of an inelastic and hypodynamic chamber. While the systolic peak exceeds

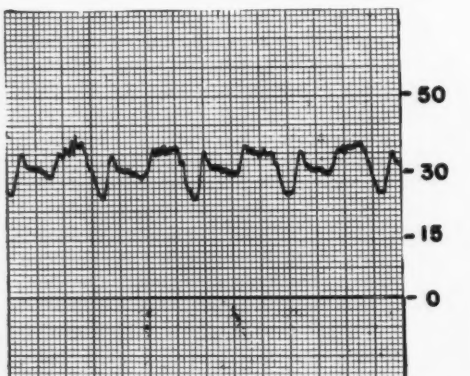


Fig. 3. Right atrial pressure curve; pressures in mm. Hg.

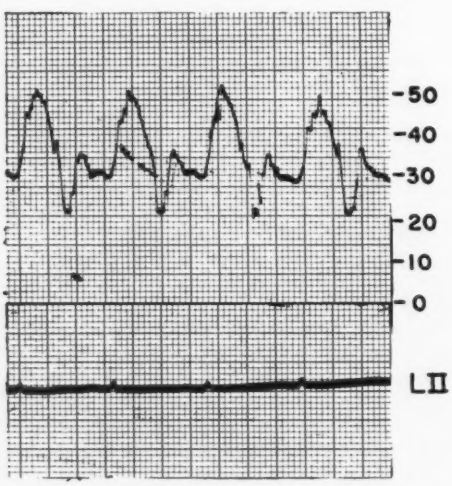


Fig. 5. Pulmonary artery pressure curve; pressures in mm. Hg.

Fig. 4. Right ventricular pressure curve; pressures in mm. Hg.

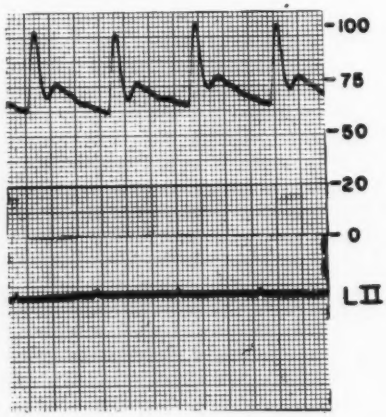


Fig. 6. Radial artery pressure curve; pressures in mm. Hg.

the normal limit, it is less than that expected in relation to the high filling pressure. There is also an early diastolic dip. This dip and consequent rise to a "diastolic plateau" reflect rapid filling of the ventricle which is due, in addition to a high venous filling pressure, to limited distensibility of the ventricle. In this patient the resting right ventricular diastolic level exceeds one-half the systolic level.

The biventricular character of the process is reflected in an abnormally elevated pulmonary "wedge" pressure. The limitation of the left ventricle is further reflected in a low systemic pressure (fig. 6) which has a narrow systolic peak in its tracing. The low systemic pressure and small systemic arterial pulse wave indicate the limitations this condition has imposed upon effective stroke output.

The cardiac output at rest and on mild exercise is markedly decreased (table 1). The stroke volumes are about one-third of normal. These findings are indistinguishable from those of constrictive pericarditis.

The apical presystolic murmur and dilatation of the left atrium were undoubtedly due to the mitral stenosis secondary to amyloid infiltration. This could have contributed to the high capillary venous "wedge" pressure and limitation of cardiac output. It is impossible to distinguish this from the effect of the infiltration of the left ventricular myocardium, but the postmortem findings do not indicate enough anatomical change in the mitral valve to have caused this rise. Catheterization studies could only be interpreted as due to an encasing lesion involving both ventricles.

TABLE 1.—*Catheterization Data*

	Pressures, mm. Hg.	
	Rest	Exercise
Right Atrium	(25)	(28)
Right Ventricle	43/26	
Pulmonary Artery	46/29 (35)	50/36 (39)
Pulmonary "Wedge"	(24)	
Radial Artery	92/61 (68)	
Arterial Oxygen		
Content	12.75	
Capacity	13.65	
Saturation	93%	93%
Oxygen Cons. cc/min.	179	224
Heart Rate	90	100

Cardiac Output	L./min.	Stroke, cc.	Index, L./M.²/Min.*
Rest	1.88	20.9	1.17
Exercise	2.13	21.3	1.33

* B.S.A. = 1.6 M.².

The diagnosis in this case could have been established by skin biopsy of the purpuric areas had this been done.[9] The skin lesion and the large tongue should have suggested the diagnosis but these findings become more prominent in retrospect than at the time of examination. The auscultatory evidence of mitral stenosis could have been more easily explained on the basis of amyloidosis than constrictive pericarditis, since valve deformities have been described in primary amyloidosis.[6] The interesting association of myelomatosis will be discussed elsewhere.

Conclusion

This case illustrates well the mechanical interference with cardiac function of amyloid infiltration of the myocardium. As in constrictive pericarditis, the diastolic volume is limited and, as the ventricle fills, the pressure rises suddenly to reach the end-diastolic pressure giving the early, diastolic "dip" and high plateau. The systolic pressure is not elevated proportionately because of interference with ventricular contraction. The resting right ventricular diastolic pressure exceeds one-half the systolic level, well within the limits described as diagnostic for constrictive pericarditis.[1]

The clinical similarity is also striking since low peripheral pulse pressure, elevated venous pressure, unresponsiveness to therapy, relatively small heart with poor pulsations and marked ascites are prominent features of adhesive pericarditis. The purpuric rash was characteristic of amyloid of the skin as described by Goltz[9] and may well have established the diagnosis ante mortem had a biopsy been done.

It would seem that any lesion which causes interference with diastolic expansion of the heart could produce intracardiac pressure patterns indistinguishable from those of constric-

tive pericarditis. This might be localized in any layer of the heart, e.g. fibroelastosis of the endocardium, myocardial amyloidosis or fibrosis and pericardial constriction due to fibrosis or neoplasm. The effect of all these processes is the inhibition of the normal elastic and contractile responses of the muscle.

Summary

A case of primary amyloidosis involving the heart is presented. The similarity of the clinical and cardiodynamic findings of this entity to the findings present in constrictive pericarditis is emphasized, and the reason for this similarity, namely, the inelastic nature of the ventricle is discussed.

Summario in Interlingua

Quando amyloide primari se infiltra a in le myocardio, il occurre un perdita de distensibilitate e un resistentia al contraction que es simile a lo que es observate in pericarditis constrictive. Le similaritate clinic inter iste duo entitates ha previemente essite notate solmente in pauc casos, e studios de catheterisation ha solmente essite executate un vice unic. Le presente reporto concerne un caso de amyloide del corde in que studios de catheterisation esseva executate. Es discutite le reationes del similaritate clinic e physiologic de iste condition con pericarditis constrictive.

REFERENCES

1 Yu, P. N. G., Lovejoy, F. W., Joos, H. A., Nye, R. E. and Mahoney, E. B.: Right auricular and ventricular pressure patterns in constrictive pericarditis. Circulation **7:** 102, 1953.

2 Hertzel, P., Wood, E. H. and Burchell, H. B.: Pressure pulses in the right side of the heart in a case of amyloid disease and in a case of idiopathic heart failure simulating constrictive pericarditis. Proc. Staff Meet., Mayo Clin. **28:** 107, 1953.

3 Fisher, D. L., Campbell, J. A., Baker, L. and Vawter, G.: Hemodynamic studies in a case of primary amyloidosis. J. Lab. & Clin. Med. **36:** 821, 1950.

4 Couter, W. T. and Reichert, R. E.: Primary systemic amyloid mimicking chronic constrictive pericardial disease. Circulation **2:** 441, 1950.

5 Findley, J. W., and Adams, W.: Primary systemic amyloidosis simulating constrictive pericarditis with steatorrhea and hyperesthesia. Arch. Int. Med. **81:** 342, 1948.

6 Eisen, H. M.: Primary systemic amyloidosis. Am. J. Med. **1:** 144, 1946.

7 DeWolf, H. and Clark, B. E.: Primary amyloidosis. Am. J. Clin. Path. **20:** 165, 1950.

8 Goldman, M. J. and Gerstle, B.: Primary systemic amyloidosis. California Med. **71:** 36, 1949.

9 Goltz, R. W.: Systematized Amyloidosis; review of skin and mucous membrane lesions and report of two cases. Medicine **31:** 381, 1952.

Further Observations on the Treatment of Superficial Thrombophlebitis with Phenylbutazone (Butazolidin)

By IRWIN D. STEIN, M.D.

Phenylbutazone is a potent anti-inflammatory agent. It was effective in modifying or causing the resolution of superficial thrombophlebitis in the extremities of 132 patients in whom this condition had proven refractory or difficult to manage. The short course of treatment which proved necessary to accomplish this end, makes this drug a practical and relatively safe addition to the management of superficial vein inflammation.

THE rapid subsidence of the inflammation in superficial veins of the limbs was described recently[1] in 50 patients treated with phenylbutazone.* This drug was employed because the superficial phlebitis had been refractory to other measures of treatment, or because it was so vexing a complication that the use of any rapid and effective method was felt to be warranted.

Since publishing this earlier report, 82 new patients have been added, making a total of 132 cases in which phenylbutazone was given in treatment. Our further experiences with phenylbutazone in the management of superficial thrombophlebitis are the subject of this study.

METHOD

Patients were selected for one of the above reasons. The accessibility of the inflamed veins made the diagnosis of a phlebitis an accurate one and simplified observing the effects of treatment. Color photographs at various stages in the course of the illness made convincing and permanent records.

The 132 patients were screened from a larger group, whose size was difficult to pinpoint because of the diverse sources from which they were obtained. A reasonable estimation would be that they were derived from 600 to 700 individuals who had presented themselves to their private physician, to the hospital ward or clinic with the typical findings of an acute superficial thrombophlebitis. Many, particularly in the early phase of our work, were the problem or refractory cases and had been treated to little avail by periods of bed rest with elevation of the extremity, by local applications of heat or cold, anticoagulants and/or antibiotics. Later on when it became apparent how relatively simple and safe it was to treat this condition in the manner described, more and more patients were treated with phenylbutazone from the start.

We employed a dosage recommended for the treatment of rheumatic conditions. Thus, each individual was instructed to take 200 mg. three times a day for three days and then 100 mg. three times a day for four more days or a total dose of 3 Gm. for the week. In order to prevent gastric irritation the medication was taken after meals. Patients were advised to take a proprietary antacid or a glass of milk if sourness or "acid stomach" did occur.

No patient was kept in bed unless the pain was severe enough to incapacitate him or the systemic reaction to the phlebitis made bedrest advisable. As a rule within 24 hours, most patients were able to get up and walk about; all were able to do so by the end of the second day. No attempt was made to limit fluids or salt intake for the sake of the phlebitis alone during the week of treatment although each patient was requested to drink or eat the equivalent of two oranges a day as a source of potassium ion. None of the patients studied had gout or polycythemia vera.

The many possible grave complications reported from use of the drug alerted us for early toxic reactions.[2-8] The patient was either examined daily when hospitalized or every other day if treated outside an institution. Blood counts in ambulant patients were done 48 hours after start of therapy and again on termination. In most hospitalized patients blood counts were done every day. It was felt that the short course of treatment, limited usually to one week, was an additional and satisfying safeguard. In a few instances, notably in individuals with migratory thrombophlebitis or visceral neoplasm, this form of symptomatic treatment was continued for longer periods of time to suppress or abort the development of new areas of superficial thrombophlebitis.

From the Mt. Vernon Hospital, Mt. Vernon, N. Y.

* Adequate supplies of phenylbutazone (Butazolidin) were donated by the Geigy Pharmaceutical Co.

Results

The earliest positive response to treatment is a decrease in pain which becomes apparent to the patient in 8 to 12 hours. By the end of 24 hours, the local redness and swelling overlying the inflamed vein has definitely regressed and the systemic fever, if present, is on the downgrade, usually precipitously. Further subsidence takes place in the next 24 hours and the bright redness of the phlebitic area begins to darken and lose its angry color. All patients are able to walk with little discomfort at this time. In the next few days there is gradual further resolution towards the normal appearance of the limb. The last physical sign to disappear is the indurated and thrombosed vein which may take one to two weeks to shrink down to a fibrous cord.

The early and marked regression seen 8 to 12 hours after use of phenylbutazone in the human subject corresponds quite closely to the changes seen in experimentally induced venous thrombosis.[9]

We have divided the patients studied into five groups in an attempt to indicate the association of the phlebitis with an etiologic factor:

Superficial phlebitis: (1) In varicose veins, (2) in malignant disease, (3) in thromboangiitis obliterans, (4) following intravenous injection of solutions for therapeutic or diagnostic intent and (5) in clinically normal veins of spontaneous origin as in idiopathic migratory thrombophlebitis.

Table 1.—*Results of Treatment with Phenylbutazone in One Hundred and Thirty-Two Patients*

Type of Superficial Phlebitis	No. of Cases	Resolution	
		Complete	Incomplete
In varicose veins	104	102	2
Associated with malignant disease	7	5	2
Associated with thromboangiitis obliterans	7	7	0
Due to medications, diagnostic dyestuffs or chemical irritants, locally introduced	8	8	0
In presumably normal veins*	6	4	2
Total	132	126	6

* This term is used for want of a better one, since it is obvious that the vein or its contents must be altered for thrombosis to occur. We have employed it arbitrarily to describe the spontaneous development of phlebitis in the superficial veins, where no local or systemic factor could be found

Comment

Phlebitis of the superficial veins in the arms and legs is not always a simple and easy condition to treat. On occasion, inflammatory changes may persist despite the usually effective management with bed rest, soaks and anticoagulant drugs. In coexisting conditions, such as pregnancy, congestive heart failure or pre- and postoperative states, one wishes there were some rapid and effective means of coping with this troublesome complication. We believe that phenylbutazone does this. Its use in superficial phlebitis was empiric, based upon its potent anti-inflammatory behavior, which was evident in a variety of disorders.[10-13]

Our previous experience with phenylbutazone in the management of acute superficial thrombophlebitis[1] is confirmed. The anti-inflammatory and analgesic properties of this drug have a marked influence on the course of this disorder, causing resolution of considerable degree within 24 to 48 hours of its use. This is all the more impressive because the treated patients represented a difficult and refractory group.

The superficial phlebitis was found most frequently in the patient with varicose veins. Of this group, 102 of 104 patients were treated expeditiously and effectively by a single course of treatment lasting one week or less. As the phlebitis is only an incident in the course of this disorder, more specific measures, i.e., saphenous vein ligation and stripping, were recommended after a period of convalescence. Of the two patients who responded incompletely, one later turned out to have a lymphosarcoma of the small bowel and the other a carcinoma of the uterus. These partial and incomplete responses have been found to be a

characteristic in the presence of some grave underlying disease, usually an occult malignancy which is not manifest at the start of treatment.

The second group numbered seven patients. All had malignant disease of visceral organs which was confirmed at operation or by autopsy. Two patients had carcinoma of the pancreas, three had pulmonary neoplasms, one had an adrenal gland carcinoma and one a carcinoma of the uterus. The superficial phlebitis was controlled completely in five patients by the use of phenylbutazone. In the remaining two, the phlebitic activity and systemic reaction were greatly lessened but would always flare up with the discontinuing of the drug. Administration in these instances continued as long as the patients were alive.

A third and extremely interesting group was that in which the superficial thrombophlebitis was part of active thromboangiitis obliterans. In the seven patients with this panvascular disease, the highly active anti-inflammatory properties of the drug was demonstrated. The painful and disabling phlebitis responded readily to treatment. Second attacks, which occurred months later, in four instances, were treated just as readily and with dispatch. As we have pointed out,[1] this is the first time to our knowledge that vein activity in Buerger's disease has been inhibited by medication. Incidentally, none of these seven patients had smoked for months to years prior to the onset of the superficial phlebitis. Since it would be of considerable importance to determine whether the arteritis which is of paramount interest in this enigmatic disease is similarly inhibited, our future plans include the microscopic study of block sections taken from involved areas of superficial phlebitis before and after use of phenylbutazone.

The fourth group consisted of five patients in whom the superficial phlebitis was the result of the introduction of irritants into the regional veins for therapeutic purposes. Three were patients undergoing injection of varicose veins with sclerosing solution. The inflammatory reaction had proved so violent in these instances, that modification was attempted with phenylbutazone. In each of these three instances of iatrogenic disease, the troublesome local and systemic manifestations were dramatically aborted. In the remaining two cases, the superficial phlebitis was the result of intravenous infusions in postoperative cases. Noradrenalin was the offending agent in one, and glucose in saline in the other. The involved veins were rapidly and successfully resolved with the aid of phenylbutazone.

In the six patients comprising the fifth and last group, i.e., patients with superficial phlebitis in presumably normal veins, some interesting facts came to light. Three patients had typically recurrent (migratory) superficial thrombophlebitis without clinical involvement of the peripheral arteries. In one the condition had been present for 15 years, in another for five years and in a third for two years. Each one was completely symptom-free provided a maintenance dose of phenylbutazone (100 to 200 mg.) daily was taken. The drug has been taken, therefore, for eight months, two years and two and one half years, respectively, and without incident. In connection with this long term use, it was interesting to read of similar freedom from toxicity in the management of arthritics who were maintained on minimal dosage but exposed to prolonged administration of phenylbutazone.[14] Another patient in this group developed a spontaneous phlebitis of one of the antecubital veins while receiving hydrocortone for rheumatoid polyarthritis. This and more serious vascular complications are seen not too infrequently in the course of long continued use of the corticosteroids.[15] The phlebitis responded quite promptly to phenylbutazone. The fifth and sixth patients were both women who developed spontaneous phlebitis of the antecubital vein of the homolateral arm following radical mastectomy. In the one instance, the time relationship to the operation was one and one half years, in the other five days. In neither was there clinical evidence of metastatic disease and in both the phlebitis regressed completely with phenylbutazone.

As previously stated, the major premises for limiting this study to patients with superficial phlebitis were for the sake of accuracy in diagnosis and for simplicity and convenience

in following the effects of treatment. This choice was fortunate. Had we chosen to study deep vein phlebitis, it is possible that the study might have been prematurely terminated. On the occasions when we used phenylbutazone in the treatment of the deep vein variety, the pain is definitely lessened as are the systemic reactions. However, the most prominent feature of a deep vein thrombosis, the swelling of the limb distal to the obstructed segment, remains unchanged. This is understandable because such swelling represents the engorgement secondary to mechanical plugging in the main channels of venous return rather than the localized inflammatory edema of a superficial phlebitis. We have, therefore, continued to advocate its use in the latter condition rather than in deep vein phlebitis.

Summary and Conclusions

One hundred and thirty-two patients with superficial thrombophlebitis in the extremities were treated with phenylbutazone (Butazolidin).

Although the causes of the phlebitis were varied, being associated with varicose veins in most cases, but also as part of Buerger's disease, following the intravenous administration of fluids or drugs in others or as complication or manifestation of malignant disease, the response to the drug was a remarkably uniform and rapid regression of the vein inflammation.

Treatment with phenylbutazone (Butazolidin) was limited to one week during which a total of 3.0 to 3.5 Gm. were administered. With this small and limited dosage, major toxic reactions were not seen. In a few patients, short-lived skin eruptions were seen.

With phenylbutazone (Butazolidin) treatment is simplified in that the patient remains ambulant and local management is eliminated. There were no attempts at dietary or salt and fluid restrictions. There is definite advantage in the reduction of time spent at bed rest, in disability and in economic loss. Phenylbutazone in our estimation is a valuable drug for the treatment of superficial thrombophlebitis.

Summario in Interlingua

Un gruppo de 132 patientes con thrombophlebitis superficial in le extremitates esseva tractate con phenylbutazona (Butazolidina).

Le responsa esseva un remarcabilemente uniforme e rapide regression del inflammation venose ben que le causas del phlebitis esseva diversissime. In le majoritate del casos le syndrome esseva associate con varices, sed illo etiam appareva como parte de morbo de Buerger, como sequela de intravenose administrationes de fluidos o drogas, o como complication o manifestation de un morbo maligne.

Le tractamento con phenylbutazona (Butazolidina) esseva limitate a un septimana. Durante iste periodo quantitates total de inter 3,0 e 3,5 g esseva administrate. Iste basse e breve dosage non resultava in reactiones toxic. In alicun patientes eruptiones dermatic a brevissime durantia esseva notate.

Le uso de phenylbutazona (Butazolidina) resulta in un simplification del tractamento proque le patiente remane ambulante. Nulle restrictiones del dieta, del ingestion de sal o de fluido esseva recommendate. Le methodo offere clar avantages in tanto que illo reduce le requirimentos de allectamento, le invaliditate, e le perdita economic. In nostre opinion, phenylbutazona es un droga de alte valor in le tractamento de thrombophlebitis superficial.

References

[1] Stein, I. D. and Rose, O. A.: Treatment of superficial thrombophlebitis with phenylbutazone. Arch. Int. Med. **93:** 899, 1954.

[2] Hinz, C. Agranulocytosis following use of phenylbutazone (Butazolidin). J.A.M.A. **151:** 38, 1953.

[3] Bershof, E., and Oxman, A. C.: Agranulocytosis following use of phenylbutazone (Butazolidin). J.A.M.A. **151:** 557, 1953.

[4] Stephens, C. A. L., Jr., and others: Benefits and toxicity of phenylbutazone (Butazolidin) in rheumatoid arthritis. J.A.M.A. **150:** 1085, 1952.

[5] Fishman, H. C., and Reynolds, J.: Exfoliative dermatitis following injection of phenylbutazone (Butazolidin). J.A.M.A. **153:** 642, 1953.

[6] Steinbrocker, O.: Caution in use of phenylbutazone. J.A.M.A. **151:** 143, 1953.

[7] Granirer, L. W.: Untoward effects of phenylbutazone (Butazolidin). J.A.M.A. **150:** 1332, 1952.

[8] KRAININ, P.: Gastric ulcer with massive hemorrhage following use of phenylbutazone. J.A.M.A. **152:** 31, 1953.

[9] STEIN, I. D.: Induced venous thrombosis and its modification by phenylbutazone. In preparation.

[10] KUZELL, W. C.: Phenylbutazone (Butazolidin) in rheumatoid arthritis and gout. J.A.M.A. **149:** 729, 1952.

[11] STEINBROCKER, O.: Phenylbutazone therapy of arthritis and other painful musculo-skeletal disorders. J.A.M.A. **150:** 1087, 1952.

[12] KUZELL, W. C., AND SCHAFFARZICK, R. W.: Phenylbutazone (Butazolidin) and Butapyrin, A study of clinical effects in arthritis and gout. California J. Med. & Surg. **77:** 319, 1952.

[13] BYRON, C. M., AND ORENSTEIN, N. B.: Clinical evaluation of phenylbutazone (Butazolidin), a new antiarthritic agent. New York State J. Med. **53:** 676, 1953.

[14] HARRIS, S. P., AND KLEIN, R.: Hematological observations in short and long term treatment of rheumatic disorders with phenylbutazone. New York State J. Med. **55:** 95, 1955.

[15] STEINBROCKER, O.: ACTH and cortisone as therapeutic agents in arthritis and some locomotor disturbances. Bull. New York Acad. Med. **27:** 572, 1951.

General Networks for Central Terminals in Electrocardiography and Vectorcardiography

By NATHAN MARCHAND, M.S., STANLEY A. BRILLER, M.D. AND CHARLES E. KOSSMANN, M.D.

A method is described for obtaining true orthogonal components of the heart vector by measuring the differences in potential between resistor networks which are connected to the limbs and to the back. The values of the resistors in the networks are determined by solving equations into which the scalar coefficients for the limbs and for the back are inserted.

COEFFICIENTS for defining the relationships between the manifest potential difference[1] of the heart (the heart vector[2]) and leads from the surface of the body (lead vectors[2, 3]) have been determined on models.[2, 3] The agreement in values obtained by two teams of investigators in two different parts of the world on two different models is quite remarkable.[9] Before these data can be applied clinically, one must attempt, by determining the coefficients in man, to overcome some of the objections to experiments on a model.

Execution of such clinical research poses many difficulties. Preliminary direct approaches in one dimension have been made by placing a dipole within the heart[4] or in the esophagus.[5] Theoretic solutions have been proposed by Frank[6] and by McFee and Johnston.[7] Observations by Frank,[6] based on studies of a full scale model of a man, have only the objection already mentioned. Analyses presented by McFee & Johnston[7] are based on the relationships between the "lead field" and the lead voltage. From these relationships they propose to create specifically desired leads either by cancelling out unwanted direction, flare or curvature of the lead field by combination with other leads, or by adjustment with suitable resistor networks of the lead field obtained at the surface of the body for the purpose of producing the desired field in the heart. From a practical point of view, the principal objection to these methods is the difficulty in visualizing the three-dimensional distribution of the lead field in the body. Furthermore, the last method is not likely to have appeal for the clinician since its application will probably involve the use of multiple electrodes, variable in number and location, and also involve the use of multiple resistors.

In an attempt to overcome these objections, and at the same time to elaborate on the analytic methods available for constructing accurate "null-potential"[8] electrodes, it will be shown that uniplanar central terminals ("component terminals") used in conjunction with a biplanar null-potential terminal may be used to determine the orthogonal components (x, y, z) of the spatial heart vector in man. The central terminal principle is used for several reasons. One is that vectorcardiographic reference systems which utilize it are less sensitive than those that do not to inter- and intra-individual changes in the position of the dipole.[6]

Using the general theory of heart vector projection,[9] a mathematical solution for two-dimensional and three-dimensional central terminals may be devised. The absolute values of the resistors within the networks of the terminals are not unique but the ratios of the values are, and are determined from the trans-

From the Department of Medicine, New York University College of Medicine, and the Electrocardiographic Laboratory of the Third (N.Y.U.) Medical Division of Bellevue Hospital, New York, N. Y.

Aided by grants from the Knapp Foundation and the New York Heart Association.

Dr. Briller is an Established Investigator of the American Heart Association.

fer functions* of the medium (the body). Points on the medium must be chosen with certain restrictions depending on the type of terminal desired (see below). The transfer functions of the three components can be calculated from the networks, the image space heart vector synthesized, and the true spatial vectorcardiogram created. The remaining problem of determining the transfer functions of the heart vector in the human body will be detailed elsewhere; the results can be no more accurate than the accuracy of these determinations.

It is not the purpose of this presentation to restate the general theory of heart vector projection begun by Burger and van Milaan[2] and ably elaborated by Frank.[9] The objective here is to apply the theory to the design of general networks, to obtain accurate central terminals and to show how these may be used to obtain the heart vector free of the errors inherent in calculations made from conventional surface leads.

Definition of Terms

Using the notations of Frank,[9] the equivalent heart dipole will be represented by the vector $\bar{p}$ where

$$\bar{p} = \bar{\imath}p_x + \bar{\jmath}p_y + \bar{k}p_z \qquad (1)$$

and $\bar{\imath}$, $\bar{\jmath}$ and $\bar{k}$ are the three component unit vectors.

The heart vector, $\bar{p}$, and its three scalar components p_x, p_y and p_z are functions of time. The midpotential of $\bar{p}$ is assigned the value of zero. All potentials are measured from this point and it is the potential of this point that must be duplicated at the zero potential central terminal. The potential difference, V, between it and any other point in or on the surface of the medium is given by

$$V = \bar{c}\cdot\bar{p} = c_x p_x + c_y p_y + c_z p_z \qquad (2)$$

The lead vector, $\bar{c}$, is invariant with time and is only dependent upon the boundary conditions determined by the position of the dipole and the properties of the medium.

The Central Terminal in Two Dimensions

It is unimportant to define the shape or character of the medium for which the central terminal is being determined, inasmuch as the vector, $\bar{c}$, in itself contains all pertinent data. It can properly be called a transfer function for the problem specified. It is only necessary that enough of these functions be involved and the leads which determine them chosen so that the transfer functions are basically independent as stated in the theory of orthogonal functions.[10] Roughly, in two dimensions, three points not on a straight line are needed. To be truly at zero potential the points must define a bounded plane which passes through the center of the dipole. On the other hand, if the terminal is to be used to obtain one orthogonal component of the heart vector, then it is only necessary to select the points so that the bounded plane defined by them is penetrated by the axis of the component to be defined.

Figure 1 illustrates a general two-dimensional inhomogeneous medium where three points,

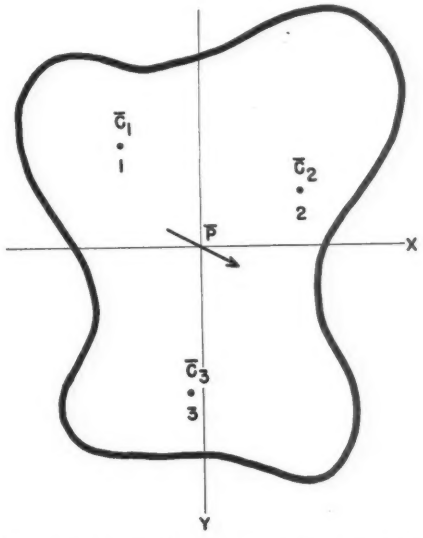


FIG. 1. A general two-dimensional medium in which three points, 1, 2 and 3, specified by their transfer functions, $\bar{c}_1$, $\bar{c}_2$ and $\bar{c}_3$, surround the potential source, $\bar{p}$.

* A "transfer function" may be described as a set of coefficients by means of which input and output quantities of any network may be related. The term is synonymous with the scalar coefficients defined in models by Burger and van Milaan[2] and by Frank.[3, 9]

1, *2* and *3*, specified completely by their transfer functions, $\bar{c}_1$, $\bar{c}_2$ and $\bar{c}_3$, will be used to determine the terminal that will have the same potential as the midpoint of $\bar{p}$. A schematic representation of the terminal circuit is illustrated in figure 2. V_1, V_2 and V_3 are the three scalar potentials obtained at the points *1*, *2* and *3*. They are measured from these points to the midpoint of $\bar{p}$. The circuit is made up of three resistors, R_1, R_2 and R_3, having respectively currents i_1, i_2 and i_3 flowing through them. The central terminal, noted as M, must have the same potential as the center point of $\bar{p}$ at all times and for all possible variations of $\bar{p}$ if it is to be used as a true null potential

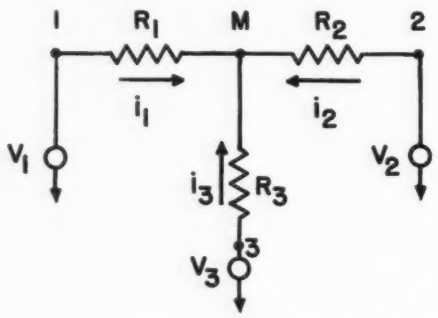


FIG. 2. Schematic representation of the two-dimensional central terminal M. V_1, V_2 and V_3 are the scalar voltages obtained at the points determined by $\bar{c}_1$, $\bar{c}_2$ and $\bar{c}_3$.

electrode. Since M must have the same potential as the midpoint of $\bar{p}$ it follows that

$$\begin{aligned} V_1 &= i_1 R_1 \\ V_2 &= i_2 R_2 \\ V_3 &= i_3 R_3 \end{aligned} \tag{3}$$

and also from Kirchoff's law that:

$$i_1 + i_2 + i_3 = 0 \tag{4}$$

Solving equations (3) and (4) will uniquely determine the resistor network for obtaining the central terminal. For (3) to be true for all values of $\bar{p}$, it has to hold for each of the components separately. Substituting (3) into (4) initially for a unit vector for $\bar{p}$ in the x direction, then for a unit vector in the y direction, two simultaneous equations are obtained.

$$\begin{aligned} \frac{c_{1x}}{R_1} + \frac{c_{2x}}{R_2} + \frac{c_{3x}}{R_3} &= 0 \\ \frac{c_{1y}}{R_1} + \frac{c_{2y}}{R_2} + \frac{c_{3y}}{R_3} &= 0 \end{aligned} \tag{5}$$

Since there are two equations with three unknowns, the absolute values of the resistors are not determined but their ratios to one another are. Solving for these ratios.

$$\frac{R_1}{R_3} = \frac{c_{1x}c_{2y} - c_{2x}c_{1y}}{c_{2x}c_{3y} - c_{3x}c_{2y}} \tag{6}$$

and

$$\frac{R_2}{R_3} = \frac{c_{1x}c_{2y} - c_{2x}c_{1y}}{c_{3x}c_{1y} - c_{1x}c_{3y}} \tag{7}$$

An example of this network can be worked out using the results for a male torso as given by Frank.[9]

$$\begin{aligned} V_1 = V_R &= -51\,p_x - 57\,p_y + 27\,p_z \\ V_2 = V_L &= 25\,p_x - 84\,p_y + 41\,p_z \\ V_3 = V_F &= -21\,p_x + 91\,p_y + 11\,p_z \end{aligned} \tag{8}$$

In this example only three points are utilized for a three-dimensional heart vector. The z component of the vector is neglected and a central terminal obtained for the two-dimensional case involving only the x and y components. Substituting into (6) and (7)

$$\frac{R_1}{R_3} = \frac{(-51)(-84) - (25)(-57)}{(25)(91) - (-21)(-84)} = \frac{5709}{511}$$

and

$$\frac{R_2}{R_3} = \frac{(-51)(-84) - (25)(-57)}{(-21)(-57) - (-51)(91)} = \frac{5709}{5838}$$

This indicates that R_2 should be made approximately equal to R_3 and that R_1 should be made approximately 11 times the size of R_3. In passing, it should be noted that these figures are in contrast to those of Bayley and Schmidt.[11] No agreement would be expected if the electric boundaries of the body, upon which the magnitude of the transfer functions in part depends, were changed by the immersion experiments done by these investigators, even though the immersion fluid was tap water.

As noted, the z component has not been taken into consideration and the central terminal obtained above will have a z component

with respect to the true midpotential of the heart vector. Only the x and y components will be reduced to zero. This point will be of considerable interest when vectorcardiographic reference systems are discussed.

The Central Terminal in Three Dimensions

In three dimensions it is necessary to specify four points with four transfer functions. This is illustrated in figure 3 where four points

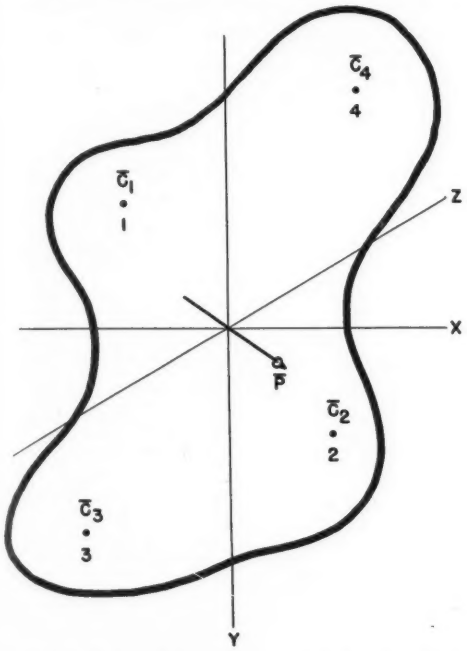


FIG. 3. Four points are shown (*1*, *2*, *3* and *4*) specified by their transfer functions ($\bar{c}_1$, $\bar{c}_2$, $\bar{c}_3$ and $\bar{c}_4$) surrounding the heart vector $\bar{p}$ situated in a heterogeneous three-dimensional medium.

(1, 2, 3 and 4) specified by their transfer functions, $\bar{c}_1$, $\bar{c}_2$, $\bar{c}_3$ and $\bar{c}_4$, surround the heart vector, $\bar{p}$.

Figure 4 shows schematically the resistor network that is used to determine the central terminal, M, which has the same potential as the midpoint of the heart vector. It now entails the use of four resistors. Again V_1, V_2, V_3 and V_4 are the four scalar potentials obtained at the points 1, 2, 3 and 4. These potentials are measured from these points to the midpoint on the heart vector. The network is now made up of four resistors R_1, R_2, R_3 and R_4 having the currents i_1, i_2, i_3 and i_4 flowing through them respectively. Since M must again have the same potential as the midpoint of $\bar{p}$, it follows that

$$\begin{aligned} V_1 &= i_1 R_1 \\ V_2 &= i_2 R_2 \\ V_3 &= i_3 R_3 \\ V_4 &= i_4 R_4 \end{aligned} \tag{9}$$

Since there is no sink or source at M,

$$i_1 + i_2 + i_3 + i_4 = 0 \tag{10}$$

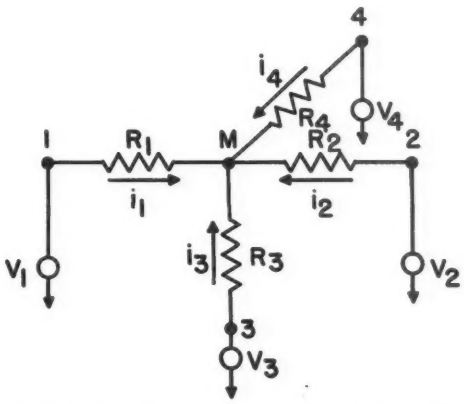


FIG. 4. A schematic representation of the three-dimensional central terminal network. M is the central terminal in a resistor network connected to four points in or on the surface of a heterogeneous medium.

As in the two-dimensional case, in order that equation (9) be true for all values of $\bar{p}$, it has to hold for each of the components separately. Substituting (9) into (10) first for a unit vector for $\bar{p}$ in the x direction, then for a unit vector for $\bar{p}$ in the y direction, and finally for a unit vector for $\bar{p}$ in the z direction, three simultaneous equations are obtained:

$$\begin{aligned} \frac{c_{1x}}{R_1} + \frac{c_{2x}}{R_2} + \frac{c_{3x}}{R_3} + \frac{c_{4x}}{R_4} &= 0 \\ \frac{c_{1y}}{R_1} + \frac{c_{2y}}{R_2} + \frac{c_{3y}}{R_3} + \frac{c_{4y}}{R_4} &= 0 \\ \frac{c_{1z}}{R_1} + \frac{c_{2z}}{R_2} + \frac{c_{3z}}{R_3} + \frac{c_{4z}}{R_4} &= 0 \end{aligned} \tag{11}$$

Since there are three equations and four resistors the ratios of the resistors to one another can be determined. Solving (11)

$$\frac{R_1}{R_4} = \frac{\begin{array}{l} c_{1x}c_{2y}c_{3z} + c_{2x}c_{3y}c_{1z} + c_{3x}c_{1y}c_{2z} \\ \quad - c_{3x}c_{2y}c_{1z} - c_{3y}c_{2z}c_{1x} - c_{3z}c_{2x}c_{1y} \end{array}}{\begin{array}{l} c_{3x}c_{2y}c_{4z} + c_{3y}c_{2z}c_{4x} + c_{3z}c_{4y}c_{2x} \\ \quad - c_{4x}c_{2y}c_{3z} - c_{2x}c_{3y}c_{4z} - c_{3x}c_{4y}c_{2z} \end{array}} \quad (12)$$

$$\frac{R_2}{R_4} = \frac{\begin{array}{l} c_{1x}c_{2y}c_{3z} + c_{2x}c_{3y}c_{1z} + c_{3x}c_{1y}c_{2z} \\ \quad - c_{3x}c_{2y}c_{1z} - c_{3y}c_{2z}c_{1x} - c_{3z}c_{2x}c_{1y} \end{array}}{\begin{array}{l} c_{3x}c_{4y}c_{1z} + c_{3y}c_{4z}c_{1x} + c_{3z}c_{1y}c_{4x} \\ \quad - c_{1x}c_{4y}c_{3z} - c_{4x}c_{3y}c_{1z} - c_{3x}c_{1y}c_{4z} \end{array}} \quad (13)$$

and

$$\frac{R_3}{R_4} = \frac{\begin{array}{l} c_{1x}c_{2y}c_{3z} + c_{2x}c_{3y}c_{1z} + c_{3x}c_{1y}c_{2z} \\ \quad - c_{3x}c_{2y}c_{1z} - c_{3y}c_{2z}c_{1x} - c_{3z}c_{2x}c_{1y} \end{array}}{\begin{array}{l} c_{4x}c_{2y}c_{1z} + c_{4y}c_{2z}c_{1x} + c_{4z}c_{1y}c_{2x} \\ \quad - c_{1x}c_{2y}c_{4z} - c_{2x}c_{4y}c_{1z} - c_{4x}c_{1y}c_{2z} \end{array}} \quad (14)$$

By using resistors of these ratios in the network a central terminal, M, can be obtained which at all times will be at the same potential as the midpoint of the heart vector.

An example of this network can again be worked out using Frank's coefficients for a male torso,[6] regarding the fourth point as being on the back.

$$V_4 = V_B = -16p_x - 13p_y + 90p_z \quad (15)$$

When this is done, using the coefficients for V_R, V_L, V_F and V_B as for the two-dimensional terminal, all the ratios have negative values as follows:

$$\frac{R_1}{R_4} = \frac{315{,}954}{-135{,}238} = -2.336$$

$$\frac{R_2}{R_4} = \frac{315{,}954}{-475{,}998} = -0.664$$

$$\frac{R_3}{R_4} = \frac{315{,}954}{-478{,}956} = -0.660$$

This can only mean that the four points chosen on the model do not include the center of the dipole. Frank's three-dimensional drawing of the image space[12] does in truth show that the dipole (center of the image space) lies anterior to the plane made by the first three points (R, L, F).

Vectorcardiographic Reference Systems

In vectorcardiography it is necessary to obtain the three components of the heart voltage in as pure a form as possible. When the transfer functions are known, it has been shown that the components of the heart vector can be obtained from the scalar voltages measured at the surface of the heterogeneous medium by means of simultaneous equations.[2, 6] This is awkward and makes the problem of obtaining the components in "real time" a difficult one. "Real time" means the instant at which they occur in the body. The central terminal in three dimensions gives an electric terminal which is at zero potential for all components, provided the image space, delimited by the four points selected in the medium, surrounds the source of potential.

A terminal remains to be obtained at which only one of the heart vector components exists. This has already been accomplished. In the example of the two-dimensional central terminal it was pointed out that the z component was completely neglected. This means that the voltage in the z axis will not be zero at this two-dimensional central terminal and the difference in potential between this terminal and the true central terminal should consist of only the z component. The actual amplitude of the component may be calculated very simply once the network has been established.

General Vectorcardiographic Network

In the general case, in addition to the three-dimensional central terminal shown in figure 4, three other two-dimensional central terminals have to be determined. These are illustrated in figure 5. A superscript is employed at the central terminal and on the resistors involved which designates the component which is to be obtained from that network. Three terminals are employed for each of the two-dimensional circuits. They can be con-

nected to different combinations of points, as shown in the figure, or they may be connected to the same points; or they may have various connections, depending upon how large a component is available in each case. The networks

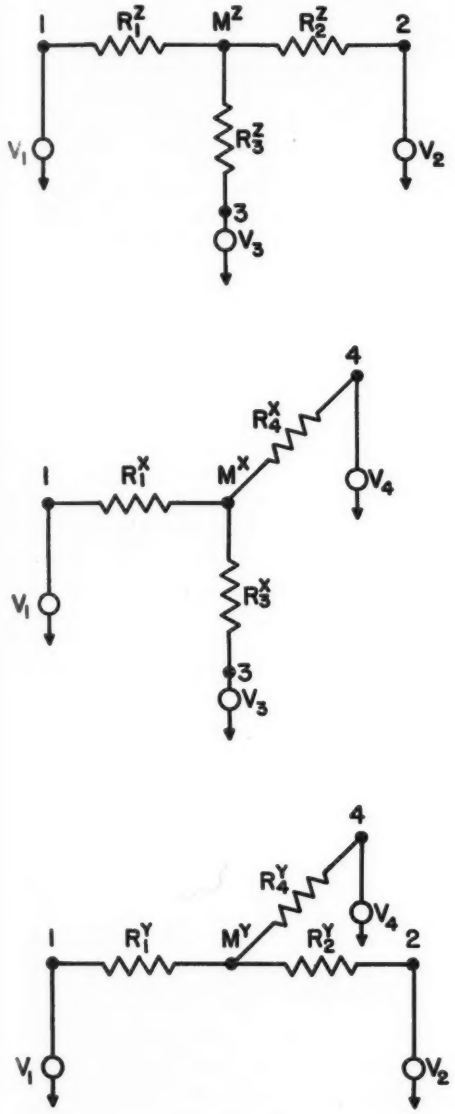


FIG. 5. For vectorcardiography, in addition to the three-dimensional central terminal shown in figure 4, three other two-dimensional (or component) terminals must be employed (see text).

are not interchangeable and have to be recalculated for each set of points used.

M^z is the "component" terminal for z. The resistors R_1^z, R_2^z and R_3^z have been chosen in the ratios specified by the two-dimensional central terminal equation (8), so that the x and y components are zero at M^z. This means that between M^z and the central terminal, M, only the z component exists. It should be noted again that the three points for a two-dimensional terminal must define a plane through which the axis of the component to be determined must pass. By calculating the difference in potential that exists between M^z and M for a unit voltage, P_z, substituted for the heart vector, it is possible to obtain the transfer function for the z component that appears at M^z. Since this voltage only has one component, the transfer function can be designated by a scalar, c^z. Similarly the transfer function for the x component voltage which appears between M^x and M, designated as c^x, and for the y component voltage which appears between M^y and M, designated as c^y, can be obtained.

$$\begin{aligned}
&\text{Voltage between } M^x \text{ and } M = V_x = c^x\, p_x \\
&\text{Voltage between } M^y \text{ and } M = V_y = c^y\, p_y \quad (16) \\
&\text{Voltage between } M^z \text{ and } M = V_z = c^z\, p_z
\end{aligned}$$

Solving for the heart vector components,

$$p_x = \frac{V_x}{c^x} \qquad p_y = \frac{V_y}{c^y} \qquad p_z = \frac{V_z}{c^z} \quad (17)$$

The values of the transfer functions of the component terminals may be readily taken into account in a practical application by means of fixed amplification or attenuation of the component terminal voltages. The resultant heart vector can then be used to generate the true, spatial vectorcardiogram.

SUMMARY

Using the general theory of heart vector projection, a general solution for both two-dimensional and three-dimensional central terminals is given. Examples of the networks, using Frank's coefficients determined from models, are given.

In the case of the two-dimensional terminal

only two of the three (x, y, z) components of the heart vector can be balanced out. The third component will affect that terminal then referred to as a "component terminal." Between the component terminal and the three-dimensional central terminal voltages proportional to the unbalanced component of the former can be obtained. By calculating the transfer functions for the respective component terminals it is possible to obtain the true components of the heart vector for vectorcardiography.

As better methods for determining the transfer functions or scalar coefficients for leads from points on the surface of the human body are developed, the resultant voltages obtained from the networks suggested should closely approach those of the true heart vector within the limits of the assumptions made in the general theory of projection of this vector.

Summario in Interlingua

Es describite un methodo pro obtener ver componentes orthogon del vector cardiac per mesurar le differentias de potential inter retes resistential que es connectite con le extremitates e con le dorso. Le valores del resistentias in le retes es determinate per solver equationes in le quales le coefficientes scalar pro le extremitates e pro le dorso ha essite inserite.

REFERENCES

[1] Einthoven, W., Fahr, G. and de Waart, A.: Über die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms. Arch. f. d. ges. Physiol. **150:** 275, 1913; Am. Heart J. **40:** 163, 1950 (translation).

[2] Burger, H. C. and van Milaan, J. B.: Heart vector and leads. Brit. Heart J. Part I. **8:** 157, 1946; Part II. **9:** 154, 1947; Part III. **10:** 229, 1948.

[3] Frank, E. and Kay, C.: Frontal plane studies of homogeneous torso models. Circulation **9:** 724, 1954.

[4] Butterworth, J. S. and Thorpe, J. J.: An evaluation of the Einthoven triangle theory. Circulation **3:** 923, 1951.

[5] Abildskov, J. A., Burch, G. E. and Cronvich, J. A.: The validity of the equilateral tetrahedron as a spatial reference system. Circulation **2:** 122, 1950.

[6] Frank, E.: A direct experimental study of three systems of spatial vectorcardiography. Circulation **10:** 101, 1954.

[7] McFee, R. and Johnston, F. D.: Electrocardiographic leads. I. Introduction. Circulation **8:** 554, 1953; II. Analysis. **9:** 255, 1954; III. Synthesis. **9:** 868, 1954.

[8] Burger, H. C.: The zero of potential: a persistent error. Am. Heart J. **49:** 581, 1955.

[9] Frank, E.: General theory of heart-vector projection. Circulation Research **2:** 258, 1954.

[10] Marchand, N.: Analysis of multiplexing and signal detection by function theory. Record of the Institute of Radio Engineers National Convention, Part **8:** 48, 1953.

[11] Bayley, R. H. and Schmidt, A. E.: The problem of adjusting the Wilson central terminal to a zero of potential in the living human subject. Circulation Research **3:** 94, 1955.

[12] Frank, E.: The image surface of a homogeneous torso. Am. Heart J. **47:** 757, 1954.

Dynamic Comparison of Current Ballistocardiographic Methods

Part II. Effect of a Platform in Ballistocardiographic Dynamics

By Samuel A. Talbot, Ph.D and W. Kirby Harrison, Jr. M.E.

Part I dealt with dynamic arrangements (Dock, Smith, Walter, Nickerson, Burger, v. Wittern) which could be treated approximately as single masses in the lower frequency range. It was shown that in addition to the cardiovascular forces sought, other undesired forces from the support were mixed in, seriously altering the record: especially for components in the important 4 to 8 cycles per second region. Second, emphasis was laid on the several meanings that could be assigned the displacement, velocity and acceleration (DVA) records, according to what dynamic aspect (motion, momentum or force) of the cardiovascular action they were *referred*. It was explained that all direct-body and stiff-bed ballistocardiographic records were "compound", as they could not be referred to any one of these dynamical quantities.

In part II, we will discuss the platform methods in detail, showing how the platform mass comes into the record. The arguments for and limitations of the various platform methods are considered, including the "shin-platform" and the very light pendular platforms now being tried.

BEGINNING with the early work of Gordon[9]* and Henderson[11] ballistocardiographers have used a platform to support the body. However, for clinically recording displacements, to limit the swinging due to respiration, restoring springs were added, minimal (Nickerson) or relatively stiff (Starr, Brown). To avoid internal flexures and oscillations, the platforms were made strongly and weighed 35 to 100 pounds. The ballistocardiograph records from such equipment could be calibrated, and showed high reproducibility and clear clinical relationships on a statistical basis.[30, 31, 32]

Such a platform with its body coupling has now been shown quantitatively[25, 28] and qualitatively[5, 33] to act as a massive transmitting element or distorting filter interposed between force on body and the pickup. The more recent "direct-body" method[6] was supposed to avoid the distortion due to such massive intermediates. In this section the distortions of the ballistocardiogram by these methods are compared quantitatively. It will appear that all the current platform methods still alter the form in some degree and confuse the interpretation of the BCG by evoking passive oscillations of the body on its support. Several methods of reducing these irrelevant forces and motions will be analyzed.

Case A. Force Applied to Platform

The problem of calibrating the Starr platform led us to investigate the platform response, y_p, to a calibrating force, F_p, with change of frequency. We measured this transmission "spectrum", y_p/F_p, experimentally as follows[28] for the high-frequency bed.

Experimental Method:

The platform (with subject on it) was shaken through the range 1 through 25 cycles per second with a device[A4]* giving constant sinusoidal force, F_p. The displacement, y_p, of platform, m_p, referred to ground (fig. 2*A*) was recorded at an amplitude of about 10 times the subject's ballistocardiogram. When plotted against frequency (solid curve, fig. 2*D*) this curve showed two simple peaks, suggesting the system frequencies of a simple two-mass oscillator. Since the platform constitutes one mass, the other should be the body. This observation confirms v. Wittern's[33] inde-

* References 1 through 29 and appendix A1 through A6 were published with Part I, Circulation 12: 577 (Oct.), 1955.

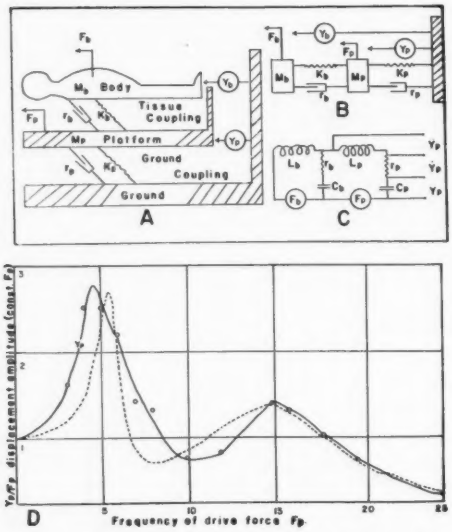


FIG. 2. Mechanical analog of the body-bed ballistocardiograph system. *A*. Distributed tissue elasticity (dorsum and feet) lumped in k_b. Distributed tissue viscosity (shear and compression) lumped in r_b. Distributed mass assumed lumped as shown. *B*. Components rearranged to show derivation of exact electrical analog, *C*, regarded as a computer, wherein driving force (voltage) is applied to either body or platform, and $y_p=D$ $\dot{y}_p=V$ $\ddot{y}_p=A$ are read as voltages. *D*. Solid line: (experimental) response of platform y_p when shaken by F_p through ballistocardiograph spectrum (1 to 25 cycles per second). Dotted line: (theoretical) response computed by *C* for mechanical analog of body and bed, *A* or *B*.

pendent demonstration that the body alone when shaken as a whole from the dorsal surface oscillates much like a single unified mass in this frequency range. It follows that the parameters of body and platform put into equations of such a two-mass system should enable us to calculate y_p/F_p and compare this theoretical response with the measured frequency response of the body-bed system. The actual calculation was made by driving an exactly analogous electrical system[A6] (fig. 2*C*) with force $E_p \sim F_p$ (putting $E_b \sim F_b = 0$).

Results: We have found by repeating this experiment with several individuals that the platform response, y_p/F_p, typically has two resonant peaks, or *system frequencies* f_1 and f_2. Up to 25 cycles per second these peaks may be fitted rather well by the computed behavior of a simple two-mass system with parameters of mass, spring and damping close to those measured directly from the body. The recorded *platform motion* y_p/F_p vs. frequency, agrees better with the response calculated for it than does the observed *body motion*, y_b/F_p.

Critique of curve fitting: The dotted curve (fig. 2*D*) shows the (computed) "platform" response of a simple two-mass oscillator, whose weights are exactly those of body and platform, respectively, coupled as in figure 2 and sprung to give (calculated) natural frequencies $f_b = \frac{1}{2\pi}\sqrt{k_b/m_b} = 5.5$ c/s, $f_p = \frac{1}{2\pi}\sqrt{k_p/m_p} = 14.5$ c/s. The (measured) frequencies of body, f_b, and *unloaded* platform, f_p, were 5 and 14 cycles per second, respectively, with error of ± 0.5 cycles per second. The (calculated) resonance at $f_1(\zeta = 0.19)$ agrees with (measured) damping of the body alone ($\zeta = 0.20$). The ratio of the two peaks varies considerably between individuals, depending quite strongly on the harmonic relation of f_p to f_b. This unexpected tuning effect may explain the difference in form of Starr records from various beds, and the poor correlation between amplitude and body mass of stiff-bed systems.[26]

The experimental response peak seen at 5 cycles per second is about twice as broad as that calculated from assuming the body to be a simple mass. We attribute the greater breadth to a slow decrease in the body mass which is effectively shaken, as driving frequency increases. This would gradually raise the frequency of resonance, and broaden the curve as shown. A subject of v. Wittern's[33] showed a similar effect. This broad peak more usually is subdivided: a small sub-peak near 8 cycles per second develops, especially with obese subjects, a behavior more evident in Griswold's experiment on ballistic body resonance by shaking the extremity.[34] The simple two-mass theory unexpectedly fits as far as the 25 cycle per second limit because at high frequency the heavy platform we used dominates y_p/F_p and submerges the disunity of the body.

To calculate mathematically the two modes of a damped two-mass oscillating system is much more complex[A7]* than for a single mass.[A2] The problem is simplified by considering only the two modes of vibration in one (head-foot) direction, rather than the twelve "degrees of freedom" (six of translation and six of rotation) in which two masses can oscillate. As in the case of the body alone (part I) the solution is considerably easier when expressed as a spectrum showing the steady response per unit force for each frequency. To calculate the actual ballistic (platform) *motion* we would require an explicit expression for the cardiovascular force pattern, which we do not have. In practice, the solution of y_p vs. frequency which we will use, tells more about the fidelity of the observed motion referred to the driving force, than would the solution for the motions y_b or y_p vs. time: the usual ballistocardiograph record from body or platform. Nickerson also has used the frequency approach.[2b]

To formulate the response spectrum of a two-mass system one writes down the forces (equation 2) depicted in figure 2*A*. These equations have already been given in the ballistocardiograph literature,[2, 35] but not their solutions. Since these solutions do not appear in mechanics textbooks, we derive them in the appendix[A7] in the compact dimensionless vector form.

(2) Forces on body: $m_b\ddot{y}_b + r_b(\dot{y}_b - \dot{y}_p) + y_b(y_b - y_p) = F_b$ (see fig. 2*A*)

Forces on platform: $(m_p\ddot{y}_p + r_p\dot{y}_p + k_py_p) + r_b(\dot{y}_p - \dot{y}_b) + k_b(y_p - y_b) = F_p$

The calculated amplitude of platform motion (y_p) referred to unit force on it (F_p) for any one frequency $\beta = f/f_b$ is (in vector notation):

$$(4a)\quad \frac{y_p}{F_p} = \frac{\mu}{k_b}\,\frac{(1-\beta^2)+j\beta/Q}{(F^2 - A\beta^2 + \beta^4) + j\beta(B - \beta^2 C)/Q}$$

(See appendix A7 for constants, notation, and steps in solution)

This complex value may be read off at once as a voltage on a simple analog computer (fig. 2*C*); and is the equation for the dotted curve with two peaks shown in figure 2*D*. The fit of this is good enough in general to take as confirming for the present purpose the validity of two-mass mechanics for the various bed systems.

We have only shown that the body-platform system actually behaves much like a simple two-mass mechanical system, when the *platform* receives the driving force. This is probably because the full complexity of the body mechanics is not brought into play by a drive operating through the feet and dorsal tissues. Nevertheless, to a first approximation and for small motions, our evidence further confirms that the body may indeed be replaced by a simple mass on *linear* springs and dampers. For motions much larger than 10 times the ballistocardiogram this equivalence of linear dynamic elements may fail; though there is no actual evidence that it does.

Case B. Driving Force Applied to Body

Unfortunately we cannot apply a shaking force directly to the internal center of gravity, m_b. When one externally shakes a subject lying on a platform, a single-mass response in y_p/F_b can be obtained, but complicating artefacts sometimes appear. These are attributable to contact complexities of shaker at head or feet, variable coupling of subject to platform, rolling and internal modes of vibration unrelated to the pure head-foot problem at hand. These are specially evident when shaking the chest of a supine subject.[2] Since one cannot measure the mechanical parameters ($m_bk_br_b$) involved in these other motions and drives, the theory of them is inaccessible, and its agreement with experiment cannot yet be discussed. But since this two-mass model (fig. 2*A*) does describe adequately the motion, y_p, of the body-platform system when force, F_p, shakes the *platform*, we will now examine the experimental consequences of explicitly assuming that the same *model* applies to the motion of body and platform when force F_b shakes the body m_b directly.

Experimental method: A periodic force, F_b, on m_b is applied electrically as E_b to an exact analog[A6] of the same mechanical two-mass model (fig. 2*B*), now setting $E_p = 0$.

* Appendix 7 to 9 will be printed with part III for reasons of space. Equation 3 appears in appendix 7.

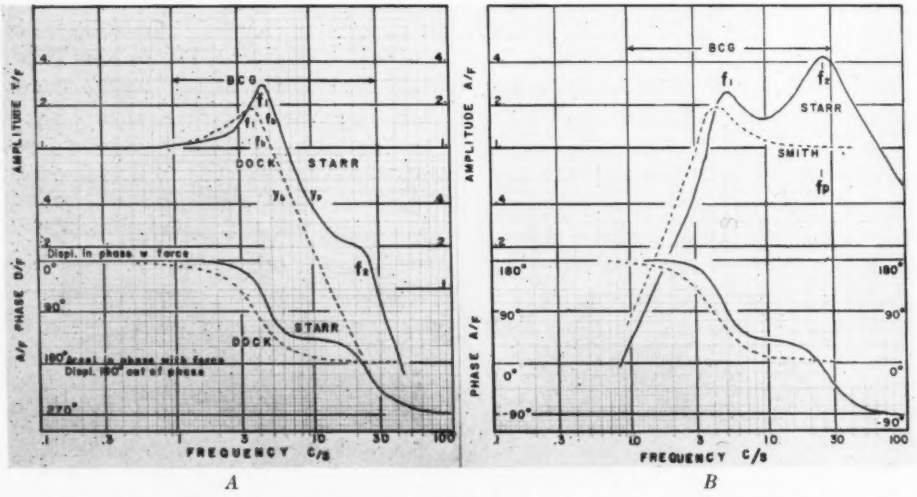
This circuit is simply a computer to solve the mechanical equations (2) for any given frequency of E_b or F_b. The platform's mechanical displacement, velocity and acceleration are proportional respectively to the voltages across C_2, R_2 and L_2 (fig. 2C); phase is referred to the driving voltage, E_b, analogous to force F_b. (In this spectral range a frequency factor of 50 is needed to use inductances, L, obtainable commercially).

In order to compare the various ballistocardiographic methods dynamically, we have used the bodily parameters of an average subject obtained by the "tap" method[A5], viz.: body frequency $f_b = 5$ cycles per second (with footboard) or 4 cycles per second (without) and damping ratio $\zeta = r_b/r_c = 0.25$ or 0.20 (respectively), mass $m_b g = 150$ pounds. From these one computes tissue stiffness $k_b = 375$ or 240 pounds per inch (respectively) and damping coefficients $r_b = 4.5$ pounds per inch per second as explained in part I. Different individuals vary somewhat[26] in the stiffness/mass ratio (k_b/m_b), or in damping ratio $\zeta_b = \frac{r_b}{2m_b\omega_b} = \frac{1}{2}Q$ but less in body frequency $f_b = \sqrt{k_b/m_b} \div 2\pi$

For the various *platforms* the values of mass, stiffness and damping were standardized as: $m_p = 30$ pounds, $f_{p_0} = 1.5$, 25 cycles per second, $\zeta_p = 0.05$.

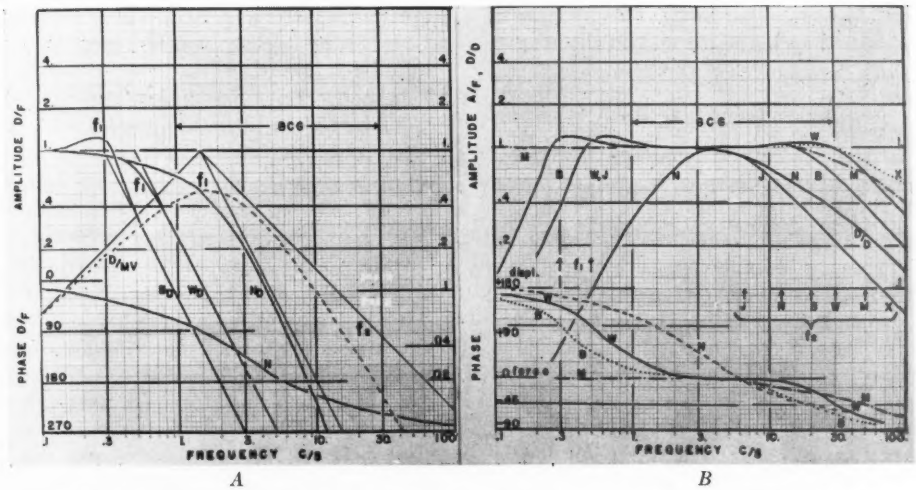
Again we emphasize that this analog computation is *not* the same as calculating the response y_p of platform when the complex body is shaken locally from *within*. The two-mass analog or approximation has been shown valid only for *external* platform shaking. The problem raised by body coupling to an internal shaker is considered in part III.

Results: The results of applying a two-mass dynamic analysis to the current ballistocardiographic recording systems appear graphically in figures 3 and 4, and analytically in equations 5a and 5b (appendix 7). These show the calculated response vs. frequency characteristics of the Dock, Starr, Nickerson and v. Wittern arrangements of body and bed throughout the ballistocardiographic spectral range. These response spectra are actual rather than theoretical, insofar as the assumption holds that the body acts as a unified mass, throughout the ballistocardiograph spectrum. In fact, this assumption is implied whenever



A *B*

FIG. 3. *A*. Response of stiff bed compared with direct body: platform displacement for constant force on body, through BCG frequency range. Illustrates (a) frequency shift at f_1 due to footboard; (b) system resonance f_1 below body frequency f_b; (c) rejection of response above 10 cycles per second, regardless of bed stiffness; (d) negligible enhancement near platform frequency and (e) phase error increasing with frequency, nonlinearly. *B*. Same as *A*, but platform acceleration compared with direct body acceleration (for constant force) vs. frequency. Illustrates (a) second system frequency peak f_2 above platform natural frequency f_p (25 cycles per second); (b) rejection of ballistic force information below 2 cycles per second; (c) range of emphasis 3 to 30 cycles per second and (d) acceleration becomes in phase with force, above resonance: dotted. Curve A $\times \omega^2 =$ (curve B).



A B

FIG. 4. *A*. Displacement/force vs. frequency for several compliant (low frequency) platform supports, e.g., Nickerson (N), v. Wittern (W), Burger (B). Illustrates (a) rejection of ballistic *force* information by *all* these; (b) lower half of ballistocardiograph range is included if N *displacement* refers to cardiovascular *momentum* (dotted) and (c) very gradual phase shift nearly proportional to frequency in N record, due to heavy damping. *B*. Acceleration/force vs. frequency for compliant supports: adding Jonnart (J) mercury (M) extra light platform (X). Illustrates (a) increased width of passband ($f_1 - f_2$) resulting from stronger body coupling to platform (W) or increasingly lighter platforms (J, N, B, M, X); (b) acceleration/force of Nickerson bed (N), being identical with displacement/displacement (D/D) for same, but both falling off at 6 decibels per octave above f_2 and (c) phase shift of W, B and M supports is negligible over ballistocardiograph range.

one thinks of the ballistic "body motion" as a *measure* of cardiovascular force. At the higher frequencies individuals probably vary more in fulfilling the assumption of a unified body: above 20 or 30 cycles per second the system probably operates in a more complex way than two masses in series.

Certain aspects of this dynamical comparison of supports have already been published by Nickerson[25] in connection with the inverse calculation of ballistic force on body. Our work agrees qualitatively with his, which is discussed in part III and appendix 9.

DISCUSSION

A. *High-Frequency Beds and the Direct-Body Method*

Figure 3*A* shows that the frequency characteristic for displacement of the Starr-type support is strikingly like that of the direct-body method, previously shown qualitatively in figure 1. The bed method has several features:

(1) Because of reproducible calibration, one may compare amplitudes between patients to some degree and for the same patient to a high degree. This reproducibility may result from the platform sensing directly the motion of the spine, as well as the legs whose coupling varies. The calibration feature is marred somewhat by resonant relations of body frequency to platform frequency, varying among patients (see above).

The use of a standard gravitational force to calibrate a stiff bed has little relation to the forces producing the ballistocardiograph record. This is because (a) the deflection of the bed for a given force on the body varies with frequency by a factor of two or three over the static value, depending on the $Q(=\frac{1}{2\zeta})$ of the patient for the major ballistocardiogram waves. (b) The platform fails to deflect to the sharper BCG details, giving nothing here to calibrate. Curve 3A indeed amounts to an evaluation of the calibration method used with the Starr bed. The usual 280 Gm weight mainly standardizes the sensitivity of the pickup in y_p/cm of record.

(2) The footboard pressure both unifies leg mass with the torso or spine, and stiffens the springy coupling of body to platform (k_b from

240 to 375 pounds per inch). This increase of f_b from 4 to 5 cycles per second on the average (fig. 3*A*) may increase the damping factor $\left(\zeta = \frac{r}{4\pi fm}\right)$, decreasing resonance $Q = \frac{1}{2\zeta}$ and so the *K* wave,[26] especially if the *I-J* interval is detuned thereby.

(3) The platform and footboard enhance response to higher frequencies not only by this frequency shift but also by adding a second response peak, f_2 (amplitude 20 per cent), emerging just above the *unloaded* platform-frequency f_p (fig. 3*A*).

No enhancement or resonance appears at loaded (deadweight) frequency (f_{p+b}). For low frequency beds this is indeed one of the system-frequencies (f_1); but when used as is customary to describe the stiff beds, the "dead-weight" frequency (f_{p+b}) has no particular relation to *either* characteristic frequency of the body-bed system. In this sense "high frequency bed" is a misnomer, as the main resonance observed, f_1, is always *below* rather than above that of the body, f_b, regardless of platform stiffness (fig. 6 and appendix 8).

(4) Respiratory weave in the displacement record is reduced by use of a platform, which averages the headward movement of the upper body and the footward movement of the lower part.[26] This averaging by the platform must also sacrifice a certain amount of ballistic force detail, if at any frequency the motion of the legs is out of phase with that of the thorax.

The net effect of these factors is an increase of nearly 60 per cent in the pass-band and improved reproducibility and stability of the ballistic displacement response of the Starr bed, over the direct-body. The increased response to higher frequencies is further significant, because the platform also reduces the random "noises" or local motions found at higher frequencies in the looser-coupled, direct-body recording. Nevertheless, both Starr and Dock methods fail to transmit high frequency ballistic information in the displacement record. That is, the two-thirds of the spectrum from 10 to 30 cycles per second is attenuated by 50 per cent or more. Hence it is not strange that Fourier analyses[25, 36] of Starr or Dock type *displacement* records do not reveal important components above 10 to 12 cycles per second, because these have been rejected before recording.

In both the stiff-bed and the direct-body methods of ballistocardiography, the body itself is so coupled to *earth* that it forms a rejection filter for motion above the resonance of this coupling. Because of this mechanical filter neither direct-body nor Starr platform records can be expected to show appreciable displacements from cardiovascular force components above 10 cycles per second. This is not true of *acceleration*, however (see below). Evidence of reliable clinical ballistocardiograph information in this upper band has been given by Smith.[19, 20]

Stiffening the platform (k_p) reduces proportionately the displacement amplitude throughout the spectrum, without greatly altering the frequency-response. (Stiffening the body coupling, k_b, is another matter, to be discussed below.) The main effect of using very stiff tables (36 cycles per second unloaded) or other supports,[34] is to so reduce the motion, y_p, being recorded, that building vibrations and electric noise become relatively large. Isolation is found useless, because isolating pads soft enough to be useful, are themselves excited by the ballistic impulses and add new errors.

We should discuss here the analyses of the direct-body (shin) ballistocardiograph as a mechanical system, given by Smith and Rosenbaum[35] and by Arbeit and Lindner.[17] Their treatment also involves two-mass mechanics, because the motion of the body is sensed via an intermediate mass, m_s, (fig. 5*B*), just as with the beds (fig. 5*A*). In most cases the force, $k(t)$, coupling the transducer (m_t) to the shin-piece, m_s, is negligible.[6, 37, 38] If this is not the case[17] the motions of the shin piece being sensed will be distorted, depending on how loosely it is fixed to the shins. An almost universal source of error in the shin ballistocardiograph is the noise entering from the floor. With sufficiently weak coupling, k_t, (photoelectric[39] or velocity coil[6]) the floor noise may be stopped either by an isolating support (k_g, fig. 5*B*) or by seismic reference.[5] This avoids the use of high-cut filters,[40] whose phase distortion may seriously affect the finer

ballistocardiograph detail. A more important source of error, unrecognized in early direct-body designs,[38] is the mass of the shin piece, m_s: which if over a few ounces[20] can significantly distort even the displacement ballistocardiogram, and radically alter the acceleration ballistocardiogram.

The analyses mentioned lead to a shin piece ("platform")[17] so light and so stiffly coupled (frequency 30 to 40 cycles per second) that it follows the shin motions (displacement, velocity or acceleration) with high accuracy. However, the record is still dominated by gross oscillatory errors from the dorsal springs, and is subject to disparity of motion between thorax and shins. With a bed platform (fig. 5*A*), m_p and k_p can be so reduced that body springs, k_b, are not excited. However, figure 5*B* shows that no adjustment of shin bar ($m_s k_s$) can cancel the effect of force k_b. Hence the most perfect direct-body pickup (wherever placed) can only sense a local portion of body motions which are already strongly distorted by the couplings to the support. We must conclude that these analyses and improvements of instrumentation have not dealt with a major problem of current clinical ballistocardiographic method: the artefact due to body gounding, almost equally large in both the direct-body and stiff bed methods.

We have already briefly mentioned experiments[8] on changing the stiffness of these "springs" coupling the body to its support. Figure 3 enables us to examine this dynamically. Foam rubber pads under the body,[8, 24] reduce k_b as well by their compliance in series, as by a slight negative stiffness (instability). The latter effect prevents reaching much below 2 cycles per second; and at the cost of greater resonance. Sinking the body in sand or putty adds more grounding springs in parallel, increasing k_b and f_b to 10 cycles per second or so. As a result the damping, $\zeta = \frac{r_b}{4\pi f m_b}$, generally decreases, again increasing the resonance peaking. However, since the major forces of the *normal* ballistocardiogram are below 12 cycles per second, the displacement record so taken does contain a wider spectrum and better resembles[41] the undistorted (mercury or pendulum) record. Nevertheless figure 3*A* shows that a shift of f_b by this amount still leaves the distortion from resonance well within the ballistocardiograph spectrum, so that the information above about 7 cycles per second still contains serious amplitude and phase error; nor is it interpretable as cardiovascular force, as explained in part I.

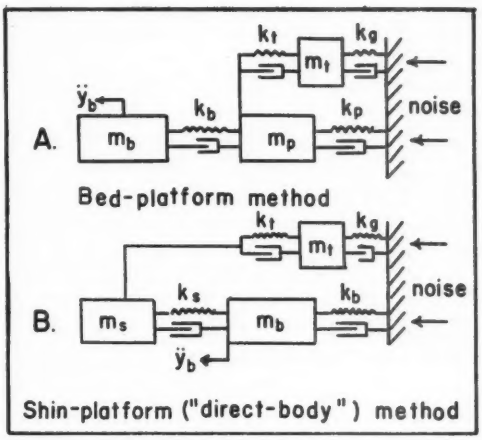


FIG. 5. Mechanics of grounding. *A*. Bed platform: adjusting k_p/m_p to minimize motion in k_b reduces noise and makes transducer read $\ddot{y}_b = \frac{m_c \ddot{y}}{m_b} c$. *B*. Shin platform (direct body): adjusting k_s/m_s to minimize motion in k_s, retains noise and makes transducer read $\ddot{y}_b = (m_c \ddot{y}_c - r_b \dot{y}_b - k_b y_b)/m_b$ or $y_b = (m_c \ddot{y}_c - r_b \dot{y}_b - m_b \ddot{y}_b)/k_b$ where $m_c \ddot{y}_c$ alone is desired. t = transducer, m_s = shin piece, k_p = platform spring, k_s = shin coupling.

In defense of raising body resonance or using resonant pickup devices, it is quite legitimate of course to enhance frequencies[20] of clinical interest. An "undistorted" rendition is not, a priori, the best possible record for all clinical ballistocardiograph purposes. If spectral analysis or trial tuning indicates that a certain region of the ballistocardiograph spectrum emphasizes pathological peculiarities, one may wish to adjust body or pickup resonance to that frequency. (This indication would be hard to attribute to a particular cardiovascular "process", because a "characteristic frequency" in the cardiac cycle is not expected in a generator whose pattern is an overlapping succession of diverse impulses from different causes.) Furthermore, the possi-

bility of *uncoupling* the body segments dynamically in a rational way rather than unifying it, raises basic questions of ballistocardiograph meaning, and is an avenue to improvement which should be thoroughly explored.[42, 43] For example, the thorax alone as a unit would be much more symmetrical for spatial (XYZ) ballistocardiographic recording than the whole body, given proper precautions against resonance and coupling between axes.

Acceleration ballistocardiograph on stiff supports. We may next consider the acceleration response curves (fig. 3*B*). By the direct-body method, the frequency-response of the body (as a filter) now covers much more of the ballistocardiograph range without distortion. If the pickup device is not tuned, acceleration, $\ddot{y}_b/F_b$, is flat above 10 cycles per second, though it still overemphasizes the major normal waves (around 4 cycles per second). However, with this direct pickup, less constancy and significance can be attached to the higher frequencies (over 15 cycles per second) because of greater bodily looseness.

If instead we interpose a stiff platform and footboard between body and ground (Starr), the platform acceleration response still holds good (fig. 3*B*, curve S) over a wide band of frequency above resonance, with overemphasis slightly shifted to $f_b = 5$ cycles per second; it also enhances strongly the broad region around (unloaded) platform frequency ($f_p = 25$ cycles per second). However, the tremendous amplification required to get an acceleration record from such a stiff bed renders it impractical above 20 cycles per second because of "noise" in amplifiers and buildings.

Neither direct-body acceleration nor displacement, therefore, yield a promising approach to recording accurately the clinical information in the upper two-thirds of the ballistocardiograph spectrum; while both render with large error the information below 10 cycles per second.

The *phase shift* of the Dock and Starr methods according to this analysis appear in figure 3*A*. In both cases, the major waves lag the driving force by about 90 degrees or 0.06 second (¼ wave at 4 cycles per second). This varying phase lag of the ballistocardiograph displacement tracing has not usually been considered in discussing their physiological origin.[10, 44] With stiff beds the phase lag increases steadily with frequency: this would cause a nearly constant shift of the whole complex waveform. For *acceleration* the phase curve is identical, except that the scale of ordinates shifts by 180 degrees. Consequently, above 10 cycles per second the Smith acceleration record is in phase with the force driving the body, but becomes 0.06 second out of phase with force for the classical ballistocardiograph components around 4 cycles per second (a 90 degree phase lead).

The *"torsional"* ballistocardiograph, as now known,[45] is based on a stiff-bed system, dynamically resembling the Starr, but in the rotational mode. The high-frequency losses of this kind of ballistocardiograph, in terms of angle of rotation, would therefore resemble that of the heavy "high frequency bed" in the head-foot record, for the same reasons. That is, body coupling to the massive support used would cut off the upper frequency range, and distort the lower range of the torsional ballistocardiogram in a similar way.

The principles discussed here, should apply equally to the *lateral* ballistocardiogram. If so, the "normal" periodicity seen in the lateral ballistocardiogram from direct-body or stiff platforms,[42, 43, 46] is also mainly an artefact of the body support. These body oscillations would distort and conceal the detail of the cardiovascular force pattern in the head-foot direction also, though at a somewhat higher frequency. Rolling is a serious complication, analytically.

B. Low Frequency Beds

The low frequency bed most often used clinically is that of Nickerson: a platform of 35 to 100 pounds with springs about one tenth as stiff as the body's, giving a lower-system-frequency, $f_1 = \frac{f_b}{\sqrt{10}} = 1.5$ c/s.[A8] Its displacement-response, N_D (fig. 4*A*), referred to driving force falls to 10 per cent at 4 cycles per second. Hence the rapid forces of Starr's *HIJ* sequence cannot be followed without lag by this slow oscillating system. Even at 1.5 cycles per second, body and platform lag the cardiovascular force by 90 degrees or 0.37 sec.; at 6 cycles per

second the platform would move 180 degrees out of phase (fig. 4*A*) with the driving force.

This unfavorable relation of the ballistocardiographic *displacement* record to cardiovascular *force* characterizes all the low frequency beds (fig. 4*A*); actually, however, they are not designed for this purpose. When the natural frequency of an oscillator is below most components of the drive frequency, as in this case, the acceleration becomes the measure of the *force*. But if referred* instead to the *displacement* of cardiovascular mass, the Nickerson displacement record renders the ballistocardiograph spectrum rather well, in both amplitude and phase (curve D/D in fig. 4*B*). Since the method in fact correlates well with stroke volume in young normals, the displacement of this particular volume of blood must be a fairly distinct motion during ejection. Apparently with the more complex ballistic force patterns accompanying atheroma[24] other cardiovascular masses also move appreciably in early systole, confusing the correlation.

The Nickerson displacement ballistocardiogram has further dynamical meaning. The *displacement* response may be referred to the *momentum* of cardiovascular drive by multiplying curve N_D by $\omega = 2\pi f$ (or dividing curve D/D by the same). With f_1 adjusted to 1.5 cycles per second, this response (dotted line D/mv, fig. 4*A*) declines at about 6 decibels per octave through the ballistocardiograph range. That is, it behaves like an integrator (compare the RC circuit in common use[7] to convert the velocity ballistocardiograph into displacement). Hence the Nickerson *displacement* ballistocardiograph summates or integrates the *momentum* during ejection, being especially effective for components up to 5 cycles per second, beyond which the contribution is negligible.

If an *accelerometer* were used on the Nickerson platform it would measure the *force* on the body rather well, especially with the original 35 pound platform (curve D/D in fig. 4*B*). The Nickerson *velocity* ballistocardiograph record referred to *force* would not give a favorable response $\left(\frac{V}{F} = \frac{D}{mv}, \text{dotted in fig. 4}A\right)$, the transmission curve of this system for velocity referred to momentum is again good: $(V/mv)_N$ = *curve* D/D in fig. 4*B*).

We may conclude from this analysis, that in the measurement of normal cardiac output, whether in terms of displacement or momentum, the Nickerson displacement ballistocardiograph is well designed for its purpose. Jonnart[24] has used clinically the acceleration record of a similar bed, to measure the cardiovascular force on the body. In his case, however, the rather massive platform cuts severely into the higher frequency components (fig. 4*B*, curve *J*).

Before embarking on a dynamical comparison of the more recent low frequency platforms of Burger, v. Wittern and Talbot, we will digress to consider the complementary nature of the *information* in ballistic vs. force records. This should be understood to appreciate the method of Nickerson.

A basic difference exists between the purposes of "ballistic" or impulse cardiography and "true" rendition of cardiovascular forces, velocities and displacements. One must choose whether to seek *summated* information or *detailed* information: i.e., the total *effect* or the changing *pattern*. Technically, the "ballistic meter"[47] operates specifically to *summate* the momentum or impulse[A1] of effects which are too rapid to follow in detail. This integration of momentum can be done by sensing the velocity (body momentum) then integrating electrically by an RC circuit (Dock); or by sensing displacement after integrating mechanically by a heavily damped mass with negligible spring (Nickerson).

The body on a 1.5 cycles per second suspension is a ballistic meter of this type because the heavy damped platform has a frequency response falling uniformly (6 decibels per octave) with frequency[25] (fig. 4*A*, dotted D/mv). If the platform moved with the body through the ballistocardiograph spectral range, and if the body moved as a whole, the Nickerson *displacement* record would trace the *integral* of the cardiovascular *momentum* pattern applied to the body for each event:

$$m_b y_b = \int_{t_0}^{t} m_c \dot{y}_c \, dt,$$

where m_c and $\dot{y}_c$ both vary continuously. Its displacement record (not area) in the I-J interval then measures the *summated* momentum or moment of stroke volume. [Above 6 cycles per second the uncoupling of the heavy platform changes the integration from first to second order (fig. 4*A*, dotted) but the amplitude here is negligible.]

* See Part I.

If the information resulting from such integration proves useful clinically, and the small details unimportant, an integrating recorder should indeed be used for this purpose. If in other cases the information from wave form proves more useful, then the response *pattern* should *not* be integrated by platform damping (m/r) or condensers (RC) but left to show its whole frequency range. Apart from this empirical view, there remains also the physiological problem of relating these detailed vs. integrated aspects of the body motion to the dynamics of blood flow in normality and disease. We should clearly recognize that the Nickerson bed *integrates* momentum prior to the transducer, and so differs intrinsically in purpose and method from most other BCG supports which aim at displaying force, the derivative of momentum. Calibrating this bed in terms of force[2] leads naturally to misinterpretation;[18] as shown in figure 4*A* curve N_D, its response in terms of cardiovascular *force* is negligible.

C. Subfrequency Ballistocardiographic Methods

Since 1952 Jonnart,[24] Burger,[4] v. Wittern,[5] Talbot,[12] and Rappaport[23] have described systems for body support, so compliant that (a) the spring coupling of platform to ground is less than one fiftieth the stiffness of the body springs, and so excites them negligibly; (b) the fundamental resonance (fig. 4*B*: f_1) is placed an octave or more *below heart frequency*, the basic component of the ballistocardiogram.[4] Burger has recorded platform motion as a measure of the displacement of cardiovascular material (y_p/D_{cv}); the others generally use accelerometers to measure *forces* on the body of cardiovascular origin ($\ddot{y}_p/F_{cv}$). The responses of all these methods are in general undistorted (fig. 4*B*) up to 10 cycles per second or more, and use enough platform damping or electrical filtering below 1 cycle per second to prevent resonance at respiratory frequency.

According to two-mass analysis, the methods mentioned differ mainly in their response to higher frequencies (fig. 4*B*, f_2). The heavy platform of Jonnart (curve *J*) without footboard attenuates appreciably at 10 cycles per second; Burger's 20 pound platform with footboard, at 30 cycles per second. By adding shoulder clamps, the v. Wittern 20 pound design (curve *W*) not only reduces the phase shift at f_2 = 30 cycles per second but theoretically extends a good response to 50 cycles per second for any transient body motion which is sharp enough to contain this component. The dotted lines (*M* and *X* in fig. 4*B*) are added to show the high-cut properties of 8 pound and 4 pound platforms as used on the "springless" mercury bed[27] and the 0.3 cycle per second pendulum[23] respectively.

D. Principles of Two-Mass Mechanics Applied to Ballistocardiograph Design

Insofar as the surface supporting the body fails to follow it at all ballistocardiograph frequencies, extraneous forces from the support will be mixed with the cardiovascular drive. So, regardless of the mechanical complexity in the body, the ballistocardiograph support should be designed to minimize these extraneous forces. The two-mass analysis, whatever its shortcomings, enables us to do this. We may apply to this problem the general principles of measurement with resonant devices. That is, the instrument's resonance should be located well above or below the frequency band of interest.[50]

High-frequency design. (a). A high-frequency resonant "platform" (shin piece, $m_s k_s$) connected (e.g., Dock, Smith) in *parallel* (fig. 5*B*) with the body-ground coupling, k_b, becomes part of a mechanical system whose primary resonance, f_b, is inescapably within the ballistocardiograph spectrum. Indeed this primary frequency, f_b, cannot be lifted above that spectrum even by clamping the body to ground (sand-bed),[8] due to the intrinsically low stiffness of the tissues enveloping the body. Consequently very high-frequency (stiff) coupling of the shin piece being measured[20] does not reduce the basic error from somatic oscillations. This approach not only preserves the errors around body frequency, but with the acceleration record, enhances variability in shin vs. body motion at high frequency, because of loose joints compared with footboard methods.

(b). A resonant platform (bed $m_p k_p$) may be put in *series* (fig. 5*A*) with body and ground, with relatively high-frequency coupling to the latter (e.g., Starr, Braunstein, etc.). This would seem to reduce the extraneous oscillation in the dorsal tissues, because the platform somewhat follows the body. However, because

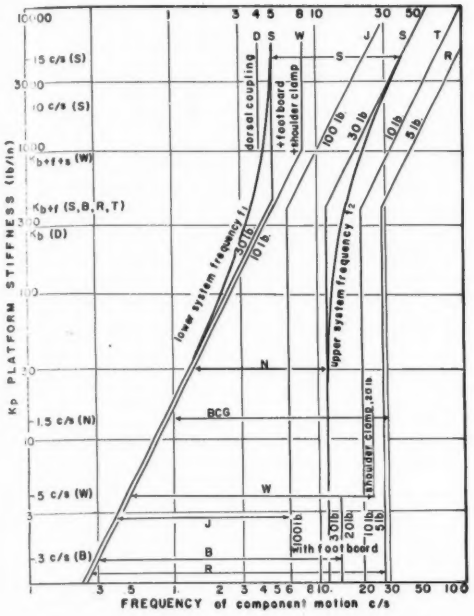


FIG. 6. Relation of *system frequencies* f_1 and f_2 to *stiffness* of platform support with 150 pound body vs. frequency. (a) When stiffness is *above* that of body: lower resonance f_1 always *below* that of body alone, or with footboard, or with further constraint (shoulders, sand). (b) Support stiffness *less* than that of body moves resonance f_1 out of ballistocardiograph range. (c) Reduced platform mass raises upper cutoff f_2 to admit high frequencies, with soft or stiff supports. (Lettering as in fig. 3 and 4, adding Starr (S), Rappaport (R), Talbot (T).)

putting the springs in series *reduces* stiffness to ground, the main resonant frequency, f_1, of the system (seen at the platform) is always *below* that of the body alone.[A7] Hence the resonance of the measuring system (including body) can never be set *above* the ballistocardiograph spectrum in a series arrangement either. Stiffening the platform spring raises the resonance f_1 symptotically toward that of the body (about 5 cycles per second with footboard). This is illustrated in figure 6, which shows how the lower and upper system frequencies of two masses in series, vary with the stiffness of platform-ground coupling.

The lines representing the system frequencies f_1 and f_2 were plotted (equation 7 in appendix 7, 8) for the simpler undamped case, since the damping ratios are relatively small. The figure includes asymptotic lines for f_1 and f_2 for several platform masses, keeping a body mass of 150 pounds. The ordinate of figure 6 is *platform stiffness*; on it are marked the values occurring with the various methods, including that of body alone. [The system frequencies have also been derived for the more general damped case (equation 6b, appendix 7) but differ negligibly.]

In a high-frequency bed as the platform-ground stiffness, k_p, becomes greater than the body-platform coupling, k_b, the dorsal tissue springs are excited ever more strongly, and the system at f_1 approaches asymptotically the case of a body on a rigid support. That is with the Starr beds, *the stiffer the platform spring, the more the record resembles that of the direct-body* (with footboard): except that the platform amplitude decreases as stiffness increases.

In both cases, direct-body and stiff platform, we find that the recording system includes the body, so that the objective of placing instrument resonance *above* the ballistocardiograph spectrum simply cannot be realized. That is, regardless of platform mass or stiffness, whether pickup is on shin or platform, the fundamental resonance, f_1, may approach but cannot exceed f_b. Intrinsic properties of superficial tissue limit f_b to possibly 12 cycles per second, right in the middle of the ballistocardiograph spectrum. Unfortunately no increase of platform frequency f_2 avoids this basic difficulty.

Low-frequency design. It follows that in designing for measurements over the ballistocardiograph spectrum, we are forced to the low-frequency measuring principle. Figure 6 shows certain general features required of such a system. The natural period of body and support should be far enough below the lowest ballistocardiograph frequency of interest (about 1 cycle per second) to avoid serious phase lag in the record. A factor of 3 or 4 is sufficient, if the platform is not damped ($\zeta < .3$) enough to introduce serious phase error.

At the upper end of the frequency range, the design of an optimal ballistocardiograph support is harder to specify. The critical factors are the mass of platform and stiffness of body coupling to it. If the body could vibrate

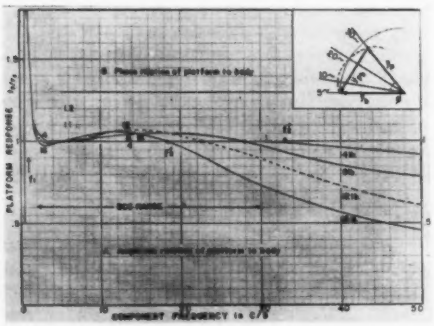


FIG. 7. *Design of a very low-frequency ballistocardiograph support. A.* Calculated for 150 pound body: lower system frequency: $f_1 < 0.5$ cycles per second; upper system frequency: $f_2 > 20$ cycles per second. If $m_b/m_p > 12$, amplitude distortion is acceptable to 40 cycles per second. *B.* Phase relations of body and platform. Although a 12 pound platform lags 50 degrees (5 milliseconds) at 30 cycles per second, and the body-platform motion, $\ddot{y}_{bp}$, is as great as that of platform, $\ddot{y}_p$, the latter still measures body-motion, $\ddot{y}_b$, within 10 per cent.

as a unit in the 20 to 40 cycles per second range, our two mass (analog) analysis shows (fig. 7) that the platform motion ($\ddot{y}_p$) measures the applied force within 80 per cent for a platform-body mass ratio of 12/150 or under. In this case the amount and distribution of phase error (50 degrees or 5 milliseconds at 30 cycles per second: fig. 7*B*, $\ddot{y}_p$) is insufficient to noticeably alter the form of fast ballistocardiogram detail. Beds of 4 to 8 pounds can be built,[23] but freedom from cross-coupled vibrational error[21] has not yet been achieved below 12 pounds.

The vibration analysis of light platforms turns out essentially that of vibrating foundations: the platform mass being shaken thru the body-spring and damper. Standard treatments of this problem[15] show graphs of high frequency response with which figure 7 agrees. The vibration of a light platform is *over-damped* by the body (i.e., $\zeta > 1, Q < .5$);[37] hence true resonance does not occur at upper system frequency in spite of a slight maximum just below the crossing at $f_2' = \sqrt{2}\, f_2$. At f_2 the relative motion of body and platform ($\ddot{y}_{pb}$) lags force by 45 degree, and $\phi_{\ddot{y}b}$ never exceeds 90 degrees.

Burger has questioned[50] whether the pickup should be placed on platform or body, since the analysis shows that at these higher frequencies, any platform moves considerably with respect to the body. He shows that at 30 cycles per second a 12 pound platform with footboard moves as much relative to the body ($\ddot{y}_{pb}$ in fig. 7*B*) as it does relative to the ground. In addition, beyond f_2 (upper resonance) the platform lags the body considerably in phase. Placing the pickup on the body rather than the platform, neatly avoids the whole question of platform error, yet retains the light, compliant support which avoids the extraneous ground forces. There are, however, several objections to putting the pickup on the patient. (a) The patient must be very quiet to avoid tremor above 20 cycles per second. (b) Accelerometers are highly sensitive to tilt, and so hard to adjust and standardize except on a stable surface. (c) In the case of left-right *LR* and anterior-posterior *AP* recording (x and z axes)[3] some sort of platform averaging of the body motion seems required for a ballistocardiograph, or else the record becomes merely a local motion.[43] (d) At high frequency the shins and spine are in phase only when a footboard or other compressive coupling is used, in which case the platform and shin ballistocardiogram become much alike.[27] (e) To record higher frequency, the shin pickup must be rigidly attached. This requires a tight bandage, which may be objectionable with certain patients. (f) The shin recording device is dynamically different for each patient.

Another escape from the difficulties of high frequency ballistocardiograph recording would be to cut off the passband at 20 cycles per second.[5, 17] With separation of the body into smaller oscillating masses above 15 cycles per second, the definition of the ballistocardiogram in this range is at issue. One may insist that the higher frequency components involve the body in such a complex way as to be quite uninterpretable and should be rejected. Unfortunately for this solution, even the normal ballistocardiogram from light beds shows many rapid consistent force details (knees, slurs, jogs and waves) which are mainly lost even with a sharp 20 cycles per second cutoff, and entirely lost with a gradual one. Characteristic ballistocardiogram features as sharp as is the Q wave (electrocardiogram) would simply be cast out. Such sacrifice of diagnostic detail, both demonstrated[20] and potential, seems hardly justified in this exploratory stage of the art. Because of the many systematic aspects, the 20 to 40 cycles per second details so recorded

cannot be relegated to transmission artefact, but should be conserved and studied. Even if two-mass theory does not strictly apply, we can conclude that the light compliant platform still minimizes irrelevant extraneous forces on the body, and serves to define for all observers a common bodily observation point for comparing ballistocardiographic events in the upper frequency range.

At present the problem of recording and studying the 20 to 40 cycle per seconds ballistocardiogram components seems beyond the two-mass analysis and remains empirical. Experience[21] shows that such details are lost with platforms weighing over 12 pounds, without coupling better than the simple footboard. In the lateral mode, the coupling problem at high frequency is much worse, and likewise the need for platform rigidity. In the head-foot mode a reasonably good wide-band ballistocardiogram is easily recorded;[23] but this, like a one-lead electrocardiogram, has intrinsic indeterminancies as a diagnostic tool.

The present state of clinical ballistocardiograph recording may be compared with electrocardiography with a single lead, recorded by an early instrument like the capillary electrometer which cut off below 20 cycles per second. The "manifest" value would not even be considered, and the range of normal records would broaden to include most abnormals. Until we have at least homogeneous data in the x, y (frontal) plane and fair detail, it is only reasonable that correlation with details of circulatory dynamics should be poor.

It would seem that a simple stretcher or light platform suspended on long wires[4, 5, 23] would fulfill these design requirements. While this is true in a crude way, we find in practice such supports, if not well developed and tested, may introduce serious extra resonances within the ballistocardiograph spectrum. The mercury bed[27] seems as yet the only method good enough for a reference standard, but more practical designs[23] have been developed to cover the ballistocardiograph passband adequately in the head-foot mode.

The ballistocardiograph pass-band. The concept of "passband for fidelity" is already familiar in terms of the electrocardiogram, recorded music, radio transmission, etc. It applies equally to the spectral range of normal and abnormal ballistocardiograph records. The "ballistocardiograph passband" has not yet been defined in any final way. If we record from a light platform on which the whole body rests in mercury, error from the support[27] is minimal, and the spectrum of maximal width. Spectral analysis of such records brings out the rapidity of clear ballistocardiogram detail and the *complexity* of reproducible pattern. A preliminary investigation of five normals and five abnormals shows[51] a significant band width reaching to 25 to 35 cycles per second for the former, to 30 to 45 cycles per second for the latter. Both theory and experiments[27] with wave synthesis show that phase shift of lower frequency components[20] will not account for such sharp details. For the present discussion, 30 cycles per second has been taken as the limit to which we wish to see the whole-body ballistocardiogram undistorted.

If, however, ballistic measurements were taken from a segment of the body (e.g., torso alone, and if certain objections thereto are met) the useful ballistocardiogram and the significant frequency limit might become appreciably higher. That is, we are not restricted to the assumption, intrinsic in some current ballistocardiograph calculations, that recording the motion of the body *as a whole* is either necessary or desirable to obtain the maximum information on the forces generated in the cardiovascular system. If we change the attack in this way, this particular analytical treatment of ballistic dynamics would also be superseded. A discussion of our current work in this direction is beyond the scope of this paper.

SUMMARIO IN INTERLINGUA

Le arrangiamentos dynamic de Starr, Nickerson, v. Wittern, e Burger involve un secunde massa—le massa del platteforma supportante. Le accopulamentos inter platteforma e corpore e inter platteforma e terra interage de maniera que le systema deveni un filtro passa-banda pro le complexo de fortias ballistocardiographic in registrationes de acceleration sed un filtro passa-basse in registrationes de displaciamento. Iste resectiones del informationes passante e le accompaniante errores de synchronisation in systemas a duo massas es subsequentemente relationate con correspondente errores de registrationes directemente ab le corpore. Es discutite le conditiones de supporto optimal pro le objectivos del ballistocardiographia a corpore integre.

The Abnormal Ballistocardiogram in Mitral Stenosis

The Relationship of the Abnormal Waves to Right Ventricular Ejection and to the Mean Pulmonary Artery Pressure

By C. B. Henderson, M.D., M.R.C.P. (Lond.)

Two abnormal waves present in the ballistocardiograms of 100 cases of mitral stenosis are described and the abnormality is classified into five grades. Evidence is presented which indicates that the abnormal waves are a result of ejection from the right ventricle and that the degree of abnormality of the ballistocardiogram bears a close relationship to the mean pulmonary artery pressure in mitral stenosis.

DESPITE the increased interest shown in the study of mitral stenosis since surgical treatment became possible, there have been few reports on the ballistocardiographic changes in this disease. Starr,[1] using a high frequency bed, described the changing size and improved form after digitalis therapy in several cases of chronic rheumatic heart disease and Starr and Mayock[2] found abnormal forms in 45 per cent of their cases of this disease. Brown and co-workers[3] described large diastolic L and N waves in some cases of mitral stenosis and Mathers and associates,[4] using a low frequency bed, secured records with bowing of the JK segments in two cases. Dock and Taubman[5] commented on the prominent L waves which sometimes exceeded the J waves on the direct body ballistocardiogram in rheumatic heart disease. In contrast to these obviously divergent results, Davis and colleagues[6] described a deformity of the late diastolic and early systolic portions of the ballistocardiograms which they found consistently in 13 of their 14 cases of uncomplicated mitral stenosis and they divided these abnormalities into four grades of severity. A similar abnormality is illustrated by de Soldati and co-workers.[9]

The large number of patients referred to the Newcastle-upon-Tyne General Hospital with chronic rheumatic heart disease provided an excellent opportunity to compare the ballistocardiograms of these patients with their clinical findings, with the results secured by cardiac catheterization, with the surgeon's impression of the lesions at operation and with the changes which resulted after mitral valvotomy.

It is the purpose of this report to describe the characteristic abnormalities of the ballistocardiogram found in the cases of compensated mitral stenosis studied. Evidence is presented chiefly in the form of simultaneous recordings of the electrocardiogram, ballistocardiogram and pressure curve from the pulmonary artery or right ventricle which provides an explanation of the genesis of these abnormal ballistocardiographic waves. The evidence indicates that the degree of abnormality of the ballistocardiogram bears a close relationship to the mean pulmonary artery pressure.

Method and Material

The diagnosis of mitral stenosis in the 100 patients studied was made by Dr. W. G. A. Swan, Dr. F. Jackson or Dr. P. Szekely in the Regional Cardiovascular Department, Newcastle General Hospital, Newcastle-upon-Tyne, on the basis of clinical, radiological and electrocardiographic findings. The sex and age incidence of the 100 patients were, 26 males

From the Regional Cardiovascular Department, Newcastle General Hospital, Newcastle-upon-Tyne, England.

The work described in this paper was supported by a grant from the Newcastle-upon-Tyne Hospital Board's Scientific and Research Sub-Committee.

aged from 21 to 50 years and 74 females aged from 17 to 53 years. Eighteen males and 52 females had normal rhythm and 8 males and 22 females had auricular fibrillation. No case clinically diagnosed as having predominantly mitral incompetence or found to have severe mitral incompetence at operation and no case of severe aortic incompetence or right ventricular failure was included in the series. The systemic blood pressure in all cases was within normal limits and in no instance did the heart rate exceed 120 beats per minute. In 23 of these cases an electrocardiogram, ballistocardiogram and pressure tracing from the pulmonary artery or right heart were recorded simultaneously and in 77 the pressures obtained at cardiac catheterization were not recorded simultaneously with the ballistocardiogram but were made under similar conditions and within 15 minutes of one another.

A high frequency Starr-type table ballistocardiograph (10 cycles per second when loaded with 150 pounds of dead weight) with a platform weight of 32 pounds, was used in the investigation and the tracings were photographically recorded on a tribeam electrocardiograph. Each record was standardised, the instrument being adjusted so that a 1 cm. displacement of the base line was produced by the application of a 280-Gm force to the platform. At first, the electrocardiogram, simultaneously recorded with the ballistocardiogram, was taken from the right arm and right leg; later the right arm and left leg were used. The *beginning* of the first deflection of the QRS complex of the electrocardiogram was utilized to time the waves of the ballistocardiogram and the pressure tracings; these times were measured to the nearest 0.01 second.

Catheterization of the pulmonary artery and right heart were performed on each patient by Dr. F. Jackson, Dr. R. E. Irvine or the author. A Southern Instrument Company recording electromanometer was used to record the pressures at the catheter tip. Repeated experiments using the same damping needle and the same length of polythene tubes as were used for catheterization, showed this apparatus to have a time lag of 0.02 second in transmitting pressure changes from catheter tip to record. A saline manometer was included in the system to permit us to obtain mean pressures at any time during the experiment and to calibrate the graphic record.

In order to avoid excitement during the catheterization and so to avoid changes in heart rate which might seriously alter both the intracardiac pressures and the form of the ballistocardiograms, the patients were given ⅓ grain (20 mg.) of Omnopon and 1/150 grain (0.4 mg.) of scopolamine one hour before the test. At first, the catheterization was performed and the pressures recorded in one room after which the patient was transported by stretcher to a room nearby where the ballistocardiogram was recorded. Later in the investigation a technique was developed by which electrocardiogram, ballistocardiogram and pressure curves were recorded simultaneously. In these experiments after a routine catheterization, the patient was transferred to the ballistocardiograph room with the catheter tip in the main pulmonary artery, the catheter being kept patent by a slow injection of saline from a 50 cc. syringe. As soon as the patient had been placed on the ballistocardiograph table the pressure pickup unit was reconnected with the catheter and simultaneous records of pulmonary artery pressure, electrocardiogram and ballistocardiogram were taken. Then the catheter tip was withdrawn, first into the right ventricle then into the right auricle and finally into the superior vena cava, the character of the pressure curve as seen on an oscilloscope indicating the position of the tip. Records simultaneous with ballistocardiograms were secured with the catheter tip in each of these positions.

Some days after these records had been secured, mitral valvotomies were performed on the 61 patients who were thought to be suitable candidates for this operation by Mr. G. Mason or Mr. S. Griffin in the Department of Thoracic Surgery, Shotley Bridge General Hospital. The surgeons noted the state of the mitral valve before and after operation and I have accepted their findings unconditionally. In 56 cases ballistocardiograms were repeated three weeks after operation.

Results

Description of the abnormal waves

In the cases of mitral stenosis investigated, small abnormal waves are superimposed on the normal waves of the ballistocardiogram. These waves are illustrated diagrammatically in figure 1, where they have been given the letters RI and RJ, the letter R being chosen because evidence will be presented suggesting that the genesis of these waves is due to events connected with right ventricular ejection. As is shown on figure 1, the position and amplitude of the extra waves are not the same on all records so that it is convenient to classify the abnormality into five grades depending on the relative distances below the base line of the nadirs of the first abnormal footward wave, RI, and the subsequent I wave. As the normal H wave is usually absent in auricular fibrillation because of the failure of effective auricular contraction, the abnormal waves are more easily seen when the auricles are fibrillating than in the presence of normal sinus rhythm. The findings in the cases having auricular fibrillation will therefore be described first.

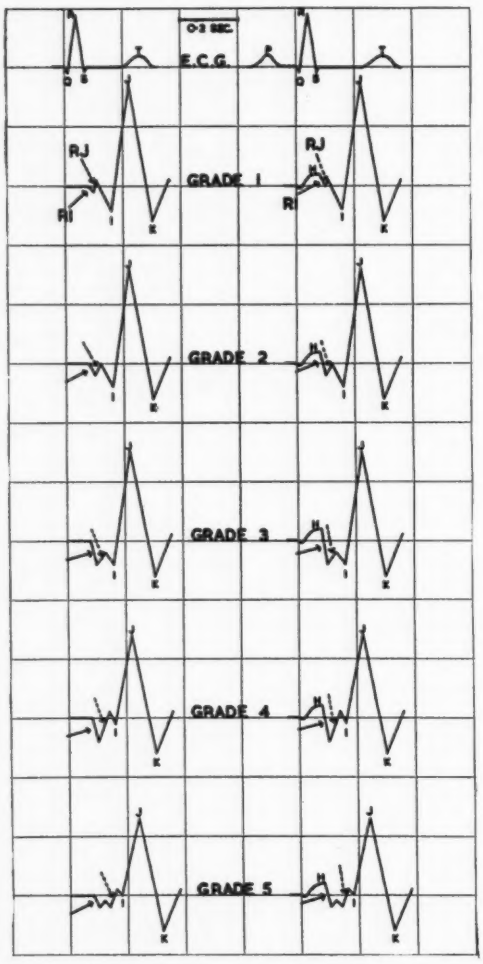


FIG. 1. Diagrammatic representation of the abnormal ballistic waves, RI and RJ, present in 100 cases of mitral stenosis. The abnormality is divided into five grades in both auricular fibrillation (left) and sinus rhythm (right). The electrocardiogram represents lead II and the time lines represent 0.2 second. The abnormal waves, RI and RJ, are marked respectively by solid and broken arrows. In a grade 1 abnormality the nadir of the RI deflection is at, or just below, the base line. In grade 2 the nadir of RI is deeper than that in grade 1 but not so far below the base line as the nadir of the I wave. In grade 3 the nadirs of the RI and I waves are at the same horizontal level and in grade 4 the nadir of RI is below that of the I wave. Grade 5 shows an additional headward and footward wave between the RI and RJ waves.

Atrial fibrillation. In what I have called a grade 1 abnormality, the first extra wave, RI, shown by the solid arrow in figure 1, is a small footward deflection which commences 0.06 to 0.1 second and has its nadir at 0.08 to 0.12 second after the *beginning* of the QRS segment of the electrocardiogram. The nadir of this deflection is usually at, or immediately below, the base line. The second extra wave RJ shown by the broken arrow in figure 1, is a small headward wave with its peak at 0.13 to 0.16 second after the beginning of the QRS segment. Immediately after this wave the downward deflection of the usual I wave of the ballistocardiogram occurs, which is followed by a headward J wave, both much larger than the abnormal waves. The footward RI wave is absent in a few records with grade 1 abnormality, and in these the first deflection is the headward RJ wave. In a *grade 2* abnormality (fig. 1) the RI wave is deeper than in grade 1 although the nadir is not so far below the base line as is the nadir of the I wave itself. In grade 3 (fig. 1) the nadirs of the RI and I waves are on the same horizontal level and in grade 4 (fig. 1) the nadir of RI is lower than that of the following I wave. Grade 5 (fig. 1) shows a more complicated picture, for an additional headward and a footward wave occur between the RI and RJ waves and the nadir of the RI wave is usually at a level lower than that of the I wave. The time interval from the QRS segment of the electrocardiogram to the beginning of the RI wave is approximately the same in all the grades of abnormality as is the interval from the QRS segment to the nadir of the RI wave. As the grade of abnormality increases, however, there is a lengthening of the time interval from the QRS segment to the top of the RJ deflection.

Sinus rhythm. In the cases of mitral stenosis with sinus rhythm studied, the abnormal waves RI and RJ occur after the normal H wave. The configuration produced by the abnormal waves superimposed on the normal waves of the ballistocardiogram permits the grouping of the abnormalities into the same five grades as described in the preceding paragraph and are diagrammatically represented in figure 1. In the

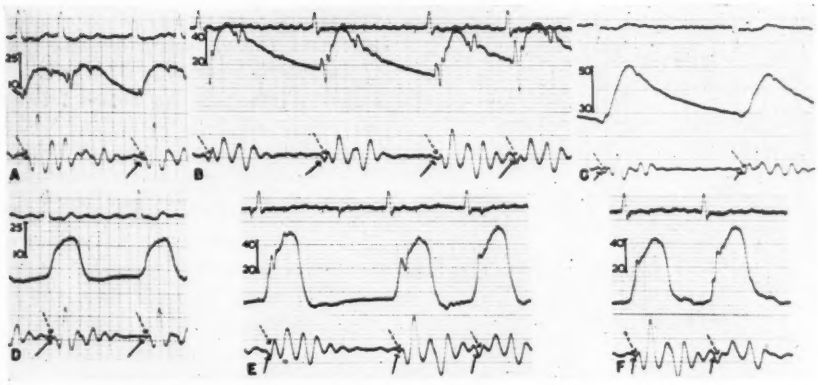


FIG.. 2 *A*, *B* and *C* are simultaneous records of electrocardiogram (top), pulmonary artery pressure (middle) and ballistocardiogram (bottom) taken from patients with mitral stenosis and auricular fibrillation. In *D*, *E* and *F* the right ventricular pressure curves are shown. The time lag in the larger pressure recording apparatus is 0.02 second. The pressure scale is in millimeters of mercury, and the time lines represent 0.1 sec., the smaller not clearly seen on some reproductions represent 0.02 second. The solid arrows indicate the RI waves and the broken arrows the RJ waves.

A—E. H., female, age 30 years. The ballistic complexes show grade 1 abnormalities. The beginning of the RI wave in each complex is synchronous with the beginning of the pulmonary artery pressure rise and the beginning of the RJ wave is 0.02 second later. The early diastolic waves of the first complex obliterate the ballistic effects of the second heart beat.

B—E. B., female, age 36 years. The ballistic complexes from left to right show abnormalities graded respectively 3, 2, 1 and 4. Note that the ballistic complex with the highest grade of abnormality follows the shortest diastolic pause and the highest end-diastolic pressure. In spite of the large artefacts in the pulmonary artery pressure curves it can be seen that the RI and RJ waves are closely related in time to the beginning of the pressure rise.

C—E. C., female, age 30 years. The first ballistic complex shows a grade 2 and the second complex a grade 4 abnormality. The grade 4 complex follows the higher end diastolic pressure. The RI wave begins at the time of commencement of the pulmonary artery pressure rise and the RJ, 0.03 second later.

D—E. H., female, age 30 years. Grade 1 ballistic abnormality. The beginning of the RI wave corresponds in time to a point approximately half way on the ascending limb of the right ventricular pressure wave.

E—E. B., female, age 36 years. The ballistic complexes from left to right show grade 2, 1 and 4 abnormalities. The grade 1 complex follows a long diastolic pause and the grade 4 complex a much shorter pause. The time relationship of the onset of RI to the right ventricular pressure curve is similar to that in *D*.

F—E. B., female, age 36 years. The first ballistic complex shows a grade 1 and the second a grade 4 abnormality. The time relationship of the RI waves to the right ventricular trace is similar to that in *D* and *E*.

subsequent text grade 5 will be described as being the most abnormal grade and grade 1 the least abnormal.

The results of the investigation show certain facts on which it is proposed to base an interpretation of these abnormal waves. It is easiest to describe the findings in auricular fibrillation and in normal sinus rhythm separately. (1). In atrial fibrillation, variation of the length of the diastolic pause is accompanied by alteration in the amplitude and timing of the abnormal waves. Figure 2*E* gives a typical example. The longer the diastolic pause the lower the classification of the abnormality when this is judged by the criteria shown in figure 1. Complexes showing grades 2, 1 and 4 abnormalities are present in the example shown in figure 2*E*, the lowest grade following the longest diastole and vice versa. This association was clearly seen in 21 records of the cases with

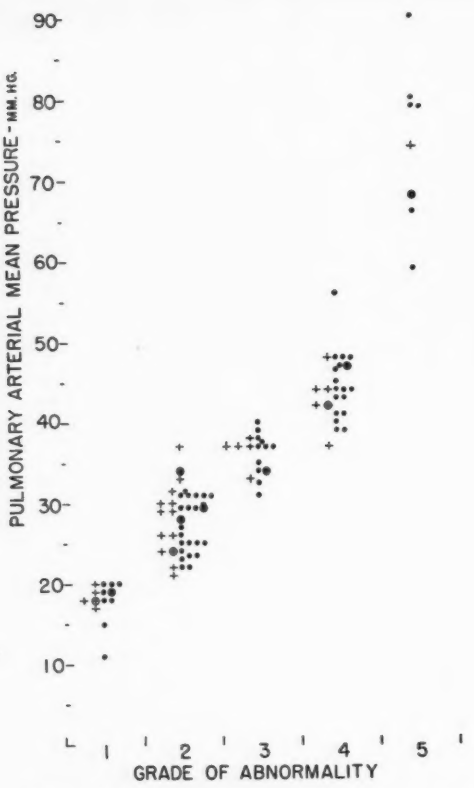


FIG. 3. The relationship between the mean pulmonary artery pressure in millimeters of mercury, and the highest grade of abnormality of complexes repeatedly seen in the ballistocardiogram of each of 100 cases of mitral stenosis. The heart rates during the pressure recording and the ballistocardiogram were closely similar. The dots represent 70 cases with normal sinus rhythm and the crosses 30 cases with auricular fibrillation. Circles have been drawn about those points which represent the grade of ballistic abnormalities of the 10 patients who were the last to be investigated in this series and in whom the ballistocardiograms were graded before the pulmonary artery pressures were known. It is seen that the mean pressures of these 10 patients fall within the pressure limits of the 90 patients investigated earlier who had comparable grades of ballistic abnormalities.

auricular fibrillation. (2) In cases with auricular fibrillation in which simultaneous records of pulmonary artery pressure and the ballistocardiogram were secured, variation in pulmonary artery pressure caused by the irregularities of cardiac force and rhythm were accompanied by corresponding changes in the positions relative to the base line of the nadirs of the RI and I waves. This is well shown in figure 2*B* where it can be seen that when the preceding end-diastolic pressure is high, the grade of abnormality of the extra waves is high and vice versa. I have records from 10 cases which show this relationship. (3) The association of the mean pulmonary artery pressure with the abnormal ballistic waves is also manifest in the 30 patients of the series with auricular fibrillation. In these, the mean pulmonary artery pressures ranged from 17 to 74 mm. Hg. The relation of the grade of abnormality of the ballistocardiogram of each patient to this pressure is not a simple one, for the grade varies from beat to beat as was described before. But, when the highest grade of abnormality of the complexes seen repeatedly in any tracing, disregarding those seen only once or twice, is plotted against the mean pulmonary artery pressure, a very close association between the two is clearly seen (crosses on fig. 3). The only exceptions to this close relationship were found in cases not included in the present series in which pulmonary artery pressures were measured at a time when the heart rate was very different from that present when the ballistocardiograms were taken. (4) In 10 cases with auricular fibrillation, ballistocardiograms were taken a few days before and three weeks after mitral valvotomy. After valvotomy, judged to be successful, the character of the abnormal waves improved in seven of the cases and they were then classified in a lower grade. An example of such improvement is shown in figure 5*C*. In the remaining three cases, the abnormal waves remained unchanged after operation.

In general, the observations recorded in sections (3) and (4) of the preceding paragraph were repeated in the 70 cases of mitral stenosis studied while in normal sinus rhythm. Additional features of these results, however, require further description. (5) In sinus rhythm the character of the abnormal waves varied with the respiratory cycle in almost all cases, an effect masked in auricular fibrillation by the greater effect of variation in duration of diastole. During expiration the grade of ab-

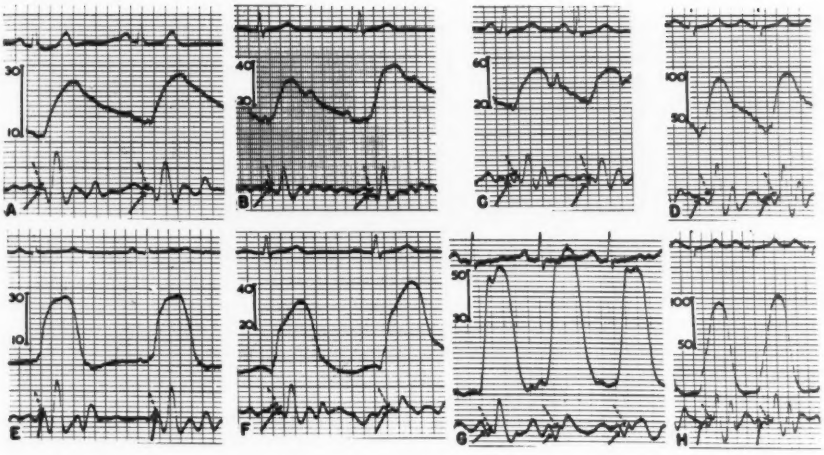


FIG. 4. *A*, *B*, *C* and *D*, are simultaneous records of electrocardiogram (top), pulmonary artery pressure (middle) and ballistocardiogram (bottom) taken from patients with mitral stenosis and sinus rhythm. In *E*, *F*, *G* and *H*, the right ventricular pressures are shown. The pressure scale, the time interval and the time lag in the pressure recording apparatus are the same as in figure 2. The solid arrows indicate the RI waves and the broken arrows the RJ waves.

A—M. O., female, age 30 years. Two ballistic complexes with a grade 1 abnormality are shown. The RI and RJ waves are closely related in time to the beginning of the pulmonary artery pressure rise.

B—B. M., male, age 43 years. Two ballistic complexes with grade 2 abnormality are shown. The RI wave begins at the time of onset of the pulmonary artery pressure rise and the RJ wave begins 0.03–0.04 second later.

C—F. C., female, age 22 years. The first ballistic complex shows a grade 3 and the second complex a grade 4 abnormality. The beginnings of the RI wave and of the pulmonary artery pressure rise are synchronous. The RJ wave begins 0.03 second later.

D—E. H., female, age 30 years. Both ballistic complexes show a grade 5 abnormality. The beginnings of the RI wave and of the pulmonary artery pressure rise are synchronous. A headward and then a footward deflection is seen between the RI and RJ waves.

E—F. S., male, age 28 years. Grade 1 ballistic abnormality. The beginning of the RI wave corresponds in time to a point approximately half way on the ascending limb of the right ventricular pressure curve. RJ begins 0.02 second later.

F—B. M., male, age 43 years. The first ballistic complex has a grade 2 and the second complex a grade 3 abnormality. The beginning of the RI wave corresponds in time to a point well up on the ascending limb of the right ventricular pressure curve.

G—V. H., female, age 33 years. Grade 4 ballistic abnormality. The time relation of the beginning of RI to the right ventricular pressure curve is similar to that shown in *E* and *F*.

H—E. H., female, age 30 years. Grade 5 ballistic abnormality. The extra headward and footward deflections between the RI and RJ waves are clearly seen.

normality of the ballistic complexes was higher than during inspiration (fig. 4C, 4F and 4G). (6) Two or more ballistocardiograms were secured from each of six patients with normal rhythm whose heart rates showed a marked difference on each record. In these, the higher rates were associated with higher grades of abnormality. Similarly, when extrasystoles occurred, the ballistic complex accompanying the premature contraction gave wave abnormalities graded higher than those following normal sinus beats. (7) As in the cases with auricular fibrillation, the records of 70 cases in sinus rhythm showed a striking relationship between the mean pulmonary artery pressure and the grading of the most abnormal complexes repeatedly seen on the ballistocardiogram, and this is shown by the dots on figure 2. This relationship existed only if the heart rates were closely similar when both investigations were made. (8) There was also improvement in the grading of 31 out of 40 cases of mitral stenosis in sinus

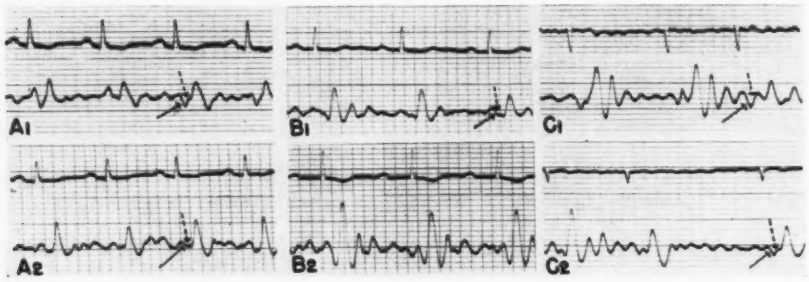


FIG. 5. Simultaneous electrocardiogram and ballistocardiogram taken from three cases of mitral stenosis before and after successful mitral valvotomy. The ballistocardiograms show improvement after operation. The electrocardiogram in *A* and *B* is from the right arm and left leg and in *C* from the right arm and right leg. The larger time lines represent 0.1 second. The solid arrows indicate the RI waves and the broken arrows the RJ waves.

A1—A. G., female, age 32 years. Sinus rhythm. Ballistocardiogram taken three days before operation. The first, third and fourth complexes show a grade 4 abnormality and the second complex a grade 2 abnormality. *A2*—Same patient three weeks after operation. Each complex shows a grade 3 abnormality.

B1—A. L., female, age 26 years. Sinus rhythm. Ballistocardiogram taken five days before operation. Each complex shows a grade 2 abnormality. *B2*—Same subject three weeks after operation. The ballistocardiogram is normal.

C1—S. P., male, age 35 years. Auricular fibrillation. Ballistocardiogram taken three days before operation. Each complex shows a grade 4 abnormality. *C2*—Same subject three weeks after operation. The graded abnormalities of the complexes from left to right are graded 2, 3 and 4.

rhythm after successful mitral valvotomy. Two examples are shown in figure 5, *A* and *B*. The data on the effect of this operation on the ballistocardiogram have not been fully assembled and will be presented in total at a later date.

Further facts about these abnormal waves became evident after studying the records secured in the 23 patients in whom electrocardiogram, ballistocardiogram and pressure curves from the main pulmonary artery or right ventricle were recorded simultaneously. Thirteen of these patients had sinus rhythm and the characteristic ballistic abnormality seen on the records was classified grade 1 in two patients, grade 2 in four patients, grade 3 in three patients, grade 4 in two patients and grade 5 in two patients. Of the 10 patients with auricular fibrillation two had a characteristic abnormality of grade 1, two of grade 2, two of grade 3 and four of grade 4. No simultaneous records were obtained from any patients with auricular fibrillation and a grade 5 ballistic abnormality.

When the time relations of the simultaneous ballistocardiograms and pressure records are compared, adjustment for the time lag in the pressure recording apparatus has always to be made. Inspecting my records, I find it easiest to make the adjustment by moving the ballistocardiogram 0.02 second to the right. As the pulmonary artery pressure tracings give a more accurate timing of the onset of ejection from the right ventricle than do the right ventricular tracings, greater emphasis will be placed on the former records when we seek to locate the onset of right ventricular ejection.

Figure 4, *A* to *D* shows typical examples of tracings taken with the catheter tip in the pulmonary artery from patients in sinus rhythm. Ballistic complexes illustrating abnormalities graded 1 to 5 are also shown. A sharp pressure fluctuation is recorded at the onset of systole in some of the pulmonary artery tracings which I attribute to movement of the catheter tip at the onset of the ventricular contraction. Despite this artefact, it is easily seen that the RI wave begins at the time of onset of the rise of pulmonary artery pressure or within 0.02 second before it and the RJ wave begins at or immediately after the onset of pulmonary artery pressure rise. When the right ventricular pressure curves are studied

(fig. 4, *E* to *H*) the RI waves are seen to begin at a time when the pressure in the right ventricle is rapidly rising and the onset of the RJ wave corresponds to a point located higher on this curve.

The tracings from the patients with auricular fibrillation (fig. 2, *A* to *F*) show the abnormal waves very clearly and disclose a similar time relationship between the RI and RJ waves and the pulmonary artery and right ventricular pressure curves.

Discussion

The abnormal waves described in this paper seem identical with those described in 13 cases of mitral stenosis by Davis and associates,[6] in one such case by Kuo and his colleagues,[7] and in one illustrated by de Soldati.[9] This more extensive investigation was designed to throw light on the genesis of these waves and their relation to the pathological physiology which results from the presence of mitral stenosis.

Kuo and his associates[7] suggested that the so-called H wave of the ballistocardiogram, sometimes seen in patients without auricular contraction, could be attributed to asynchronous ejection of the ventricles and they also noted that "double peaked" systolic ballistic complexes were encountered almost exclusively in patients, including one with mitral stenosis, in whom the electrokymogram showed a systolic pulsation of the pulmonary artery which preceded that of the aorta. Davis and coworkers,[6] seeking for an explanation of the abnormal waves, mentioned the effects of the pulmonary vascular resistance, ventricular asynchrony and the auriculoventricular gradient as possibly contributing towards the production of the abnormal early systolic waves. Later, Kuo and Schnabel[8] described similar ballistic waves in 10 cases of mitral stenosis with proven severe incompetence and suggested that the early systolic headward wave in these cases was probably produced by the backflow of blood through the incompetent mitral valve.

The results obtained in the present series of cases demonstrate clearly that the character and timing of the abnormal waves seen in mitral stenosis vary as the pulmonary artery pressure varies. Changes in pulmonary artery pressure go hand in hand with changes in the abnormal RI and RJ waves of the ballistocardiograms when heart rate changes, when the duration of the preceding diastole varies, with the changing phases of respiration and with the improvement following successful mitral valvotomy. Indeed, whenever the pulmonary artery pressure changes in any direction in the cases studied a similar change in the abnormal waves accompanies it. Therefore, the conclusion is unavoidable that the two are strongly correlated and one has the right to believe that the abnormal ballistic waves have their origin in events connected wih the contraction of the right ventricle.

The two waves, RI and RJ, by which abnormality of the ballistocardiogram may be recognized in mitral stenosis, occur both in cases with normal sinus rhythm and in those with auricular fibrillation; therefore, auricular contraction is not a factor in their genesis. In the cases with normal sinus rhythm, the footward RI wave begins immediately after the usual H wave of the ballistocardiogram; in the cases with auricular fibrillation, the H wave being absent, RI is usually the first footward deflection of the ballistocardiogram, coming 0.06 to 0.1 second after the beginning of the QRS complex of the electrocardiogram. As has been shown, the RI wave begins at, or immediately before, the onset of the pressure rise in the pulmonary artery and therefore close to the beginning of ejection into that vessel. The artefacts occurring at the onset of systole in some of the pulmonary artery pressure tracings make it impossible to define the relationship more accurately. The RJ wave is seen to begin in all cases at or shortly after the onset of pulmonary artery pressure rise, and so at or just after the onset of right ventricular ejection. As the evidence indicates that the RI wave so closely coincides with the beginning of right ventricular ejection, it seems reasonable to suggest that this wave is caused by the footward recoil from right ventricular ejection and the following RJ wave may well be due to the headward impact of ejected blood striking the curve and bifurcation of the pulmonary artery, so

that the abnormal waves are in some respects comparable to the usual I and J waves of left ventricular ejection. It is not suggested, however, that the RI and RJ waves represent the right ventricular ballistocardiogram completely. Indeed, as the pulmonary artery pressure continues to rise after the completion of the RJ wave, it seems more probable that this wave of right ventricular origin is interrupted by the footward recoil wave of left ventricular ejection; the normal I wave. In the cases of mitral stenosis investigated when the pulmonary artery pressures were only slightly above normal the RI and RJ waves were small. In the cases with high pulmonary artery pressure when ballistic complexes with abnormalities of grades 4 and 5 are seen, the position and frequently the amplitude of the RJ wave approach more closely the position and amplitude of the normal J wave. This suggests that in a high pressure system the forces generated during systole by the hypertrophied right ventricle increase in magnitude and approach in timing those produced by the left ventricle and that they influence the ballistocardiogram accordingly.

In the past, it has been assumed that the effects of right ventricular ejection are summated with those of the left ventricle in producing the I and J waves of the normal ballistocardiogram; and, except in abnormal tracings which show a bifid J wave, the effects of ejection from each ventricle cannot be separated. If, as is suggested in this communication, the abnormal waves of the ballistocardiogram in mitral stenosis, RI and RJ, are a result of right ventricular ejection, then the question to be asked is why do these waves appear appreciably earlier than the I and J waves of the same tracing. Consideration of two important differences between the anatomy and physiology of the right and left sides of the heart may help to answer this question. First, the distance from the pulmonary valve to the bifurcation of the pulmonary artery is much shorter than that from the aortic valve to the arch of the aorta. Thus, although waves in the two vessels cannot be expected to travel with an equal velocity, because of the shorter distance to travel, the headward impact when blood changes direction at the pulmonary artery bifurcation may precede that, due to blood rounding the aorta. The second difference is that the end diastolic pressure found in the pulmonary artery is much lower than that in the aorta. It is conceivable that because of this great difference, the right ventricular ejection pressure is reached sooner and right ventricular ejection occurs earlier, and the ballistic effects of this ejection are manifest earlier than are those due to left ventricular ejection. A search of the literature has failed to find any mention of simultaneous right and left ventricular pressure tracings taken in cases of mitral stenosis. However, the author had the opportunity of securing pressure tracings from both the arch of the aorta and the main pulmonary artery in a proven case of patent ductus arteriosus when the catheter tip passed through the ductus. In this case, the mean pulmonary arterial pressure was elevated above the normal, being 38 mm. Hg, while the aortic mean pressure was 83 mm. Hg. The ballistocardiogram in this patient showed abnormal waves similar to those just described in cases of mitral stenosis with a grade 3 ballistic abnormality. The beginning of the pressure rise at the arch of the aorta was 0.04 second after the onset of the pressure rise near the bifurcation of the pulmonary artery. Therefore, the ballistic effects of ejection from the right ventricle must have preceded those of left ventricular ejection in this case.

The evidence suggests that a similar asynchrony of recoil and impacts also takes place in mitral stenosis when the pulmonary artery pressure is elevated by another mechanism. This line of reasoning indicates that the occurrence and position of the abnormal ballistic waves described as RI and RJ depends primarily on asynchronism of ventricular ejection and not on any particular anatomical abnormality. In the cases I have described, the asynchronism was associated with elevation of the pulmonary artery pressure, but Scarborough and his co-workers[9] reported cases of constrictive pericarditis which showed ballistic abnormalities similar to those shown by the one case of patent ductus arteriosus and the many cases of mitral stenosis described in this investigation.

There is an important corollary to these observations. When the investigation of the mitral stenosis cases had proceeded far enough to indicate the striking relationships between the grade of abnormality of the ballistocardiogram and the mean pulmonary artery pressure (as shown in fig. 2), one could guess the height of this pressure before knowing the cardiac catheterization findings, by observing the highest grade of abnormality repeatedly seen in the ballistocardiogram and noting the pressure range of the patients previously investigated with the same abnormal ballistic grade. In figure 3 circles have been drawn about the points representing abnormalities graded in this unbiased fashion. It will be seen that they correspond well with the pulmonary artery pressures found. This relationship was only seen if the heart rates during both investigations were closely similar.

Summary

(1) Two abnormal waves present in the ballistocardiograms of 100 cases of mitral stenosis are described. These waves occur both in patients with sinus rhythm and in patients with auricular fibrillation and are named the RI and RJ waves. The RI wave is a footward deflection commencing 0.06 to 0.1 second after the *beginning* of the QRS complex of the electrocardiogram and the RJ is a headward deflection immediately following the RI and commencing 0.08 to 0.12 second after the QRS complex. In sinus rhythm these waves follow the H wave.

(2) This ballistocardiographic abnormality is divided into five grades of severity; the classification depending on the relative distances below the base line of the nadirs of the RI and the I waves. In grade 1, the least abnormal grade, the waves are very small and the nadir of the RI wave is at or immediately below the base line while the nadir of I is well below it. In grade 2, the nadir of the RI is deeper than in grade 1 but not as far below the base line as that of the I wave. In grade 3, the nadirs of RI and I are on the same horizontal level. In grade 4, the nadir of RI is further below the base than that of the I wave. Grade 5 is more complicated and shows an additional headward and footward deflection occurring between the RI and RJ waves.

(3) The grade of ballistic abnormality changes with variation in the mean pulmonary artery pressure when the heart rate changes, when the duration of the preceding diastolic pause varies, with the changing phases of respiration and with the improvement following successful mitral valvotomy. The higher the mean pulmonary artery pressure the higher is the grade of ballistic abnormality.

(4) A close correlation is shown between the mean pulmonary artery pressure and the maximum grade of abnormality of complexes repeatedly seen in the ballistocardiogram in each of the 100 cases of mitral stenosis studied.

(5) Simultaneous records of electrocardiogram, ballistocardiogram and pressure tracings from the pulmonary artery or right ventricle in 23 cases of mitral stenosis show that the RI and RJ waves are closely related in time to the commencement of right ventricular ejection. It is suggested that the RI wave is caused by the footward recoil resulting from right ventricular ejection and the following RJ wave is caused by the headward impact of ejected blood striking the curve and bifurcation of the pulmonary artery.

Summario in Interlingua

Es describite duo undas anormal incontrate in le ballistocardiogrammas de 100 casos de stenosis mitral. Le anormalitate es classificate in cinque grados. Es presentate datos que indica que le undas anormal es le resultato de un ejection ab le ventriculo dextere e que le grado del anormalitate del ballistocardiogramma es nettemente relationate al pression pulmonoarterial median in stenosis mitral.

Acknowledgment

I wish to express my thanks to Dr. W. G. A. Swan, Dr. F. Jackson and Dr. P. Szekely for permission to study their cases and to Mr. G. Mason and Mr. S. Griffin for information on the state of the mitral valves before and after valvotomy. I also wish to thank Mrs. G. Cairns for her clerical help in the follow-up of the patients studied. To Mr. D. J. Roberts I am indebted for his technical assistance in taking records during catheterization of the heart. I wish particularly to express my gratitude to Dr.

Isaac Starr for his advice and assistance in the preparation of this report.

REFERENCES

[1] STARR, I.: Clinical studies with the ballistocardiograph in congestive heart failure, on digitalis action, on changes in ballistic form and in certain acute experiments. Am. J. M. Sc. **202:** 469, 1941.

[2] — AND MAYOCK, R. L. On the significance of abnormal forms of the ballistocardiogram. Am. J. M. Sc. **215:** 631, 1948.

[3] BROWN, H. R., DE LALLA, V., EPSTEIN, M. A. AND HOFFMAN, M. J.: Clinical ballistocardiography. New York, Macmillan 1952, p. 160.

[4] MATHERS, J. A. L., NICKERSON, J. L., FLEMING, T. C. AND PATTERSON, M. C.: Abnormal ballistocardiographic patterns in cardiovascular disease as recorded with the low-frequency critically-damped ballistocardiograph. Am. Heart J. **40:** 390, 1950.

[5] DOCK, W., TAUBMAN, F.: Some techniques for recording the ballistocardiogram directly from the body. Am. J. Med. **7:** 751, 1949.

[6] DAVIS, F. W., SCARBOROUGH, W. R., MASON, R. E., SINGEWALD, M. L. AND BAKER, B. M.: The ballistocardiogram in mitral stenosis. Circulation **7:** 503, 1953.

[7] KUO, P. T., SCHNABEL, T. G. AND KAY, C. F.: On certain abnormal ballistic complexes; their relationships to other mechanical and electrical events of the cardiac cycle. Circulation **6:** 74, 1952.

[8] — AND SCHNABEL, T. G.: Certain abnormal circulatory dynamics of mitral stenosis associated with a major degree of regurgitation. Am. J. Med. **15:** 50, 1953.

[9] DE SOLDATE,. L. NAVARRO V. R. AND MEJIA R. H.: El Balistocardiograma en algunas deformidades valvulares y anomalias congenitas cardiacas. Rev. Argent. de cardiol. **18:** 189, 1951.

Three-Plane Ballistocardiography: The Effect of Age on the Longitudinal, Lateral, and Dorsoventral Ballistocardiograms

By HAROLD W. MARCH, M.D.

The motions of the thorax and of the shins were recorded by a technic which gives approximately the same size waves when a given force is applied to the thorax in each of three planes. Applied to a group of men and women under 30 years of age and another group of normals over 50, the variations in form and size of the ballistocardiographic forces in three planes were recorded. During expiration and as a result of aging, the lateral systolic wave, IJ, increases in size relative to the head-foot IJ. It is concluded that the classic head-foot ballistocardiogram yields inadequate information on the force liberated in systole, particularly in older men.

IN 1945 Hamilton and associates, in their early study of ballistic forces, utilized a high frequency bed system with freedom to record motion along the three axes of the body.[10] Although the details of the apparatus were not published, a reconstructed diagram of their records shows clearly that when the footward I wave is inscribed, leftward and anterior motion also occurs, while the headward J is accompanied by displacement of the body to the right and posteriorly. In contrast, a variable time after the peak of K, the motion of the body becomes predominantly longitudinal and only minor deflections are recorded along the other axes. By this method the authors were able to support their conviction that the IJ stroke is derived directly from the heart's forces, whereas the waves that follow are derived from forces directed along the aortic (longitudinal) axis.

Subsequently, both high- and low-frequency beds were modified for the purpose of studying motion in all planes, either by employing an accessory turntable [9, 12] or by constructing a bed with two degrees of freedom.[3a] The turntable method was not ideal, since simultaneous recording in three planes was impossible and since the position of the patient, relative to the platform, had to be changed in order to record the dorsoventral displacements. The lateral and dorsoventral traces recorded with this apparatus exhibit an I wave, directed rightward and anteriorly, and a J wave, going leftward and posteriorly. Thus, lateral motion was found to move opposite to the displacement seen in Hamilton's diagram. Dorsoventral motion was the same. Braunstein's two-dimensional high-frequency bed[3a] allows simultaneous longitudinal and lateral records to be taken, but he found that distortion from body rotation was introduced when freedom to move dorsoventrally was added. He has employed a cathode ray oscillograph to demonstrate the ballistic vector loop in the frontal plane.[3b] His records show an I wave, directed footward and rightward, and a J wave, returning headward and leftward.

In this laboratory, interest was aroused in multiplane recording for the purpose of studying the movement of the thorax in congenital heart disease with shunts of blood from left-to-right or from right-to-left.[2] Lateral and dorsoventral motion of the thorax was sensed by using electromagnetic pickups fixed directly on the right lateral and anterior chest wall. These tracings usually, but not invariably, showed leftward motion with the I wave, and rightward motion with J. It was suggested that the

From the Department of Medicine, State University of New York College of Medicine at New York City, Brooklyn, N. Y.

This work was supported by grant H-1250 (C) from the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md.

rightward I recorded from tables might be the result of body torsion, which would push the table in a direction opposite to that of the actual body movement. This system was suitable only for use when respiration was suspended, and could not be used to determine how breathing affected lateral motion.

Thus, laboratory findings and common sense indicated that ballistocardiographic motion was greatest in the thorax and it appeared that the best recording system would be one that sensed lateral and dorsoventral motion from the thorax alone. For this purpose, Dock[7] constructed a spring-opposed platform 25 by 21 inches (65 by 55 cm.) with freedom to move from side to side, contained in a frame free to move from front to back. On this platform the thorax of the supine or prone subject could be positioned. From such a platform, very satisfactory ballistocardiograms could be made, and this system has been routinely employed in this laboratory since 1953, together with the electromagnetic shin pickup for head-foot motion.[6] The information derived from this routine study has profoundly modified our concepts of ballistocardiography. The current report offers a systematic analysis of the three-plane ballistocardiograms of a group of young and elderly normal subjects.

Materials and Methods

In order to characterize the variations in form and amplitude of the lateral and dorsoventral ballistocardiogram with aging, the study included two groups of asymptomatic, presumably normal individuals. The first of these was a series of 23 men and 15 women, drawn from the house staff of Kings County Hospital. Their age ranged from 20 to 29 years and the average age for the entire group was 25 years. The mean age for either sex was approximately the same as the mean for the combined group. The second group was composed of 32 individuals between the ages of 50 and 75 years, 17 men and 15 women. The average age of these subjects was 58.5 years; for the men 59.8 years and 57 years for the women. They were selected mainly from the surgical and orthopedic wards of the hospital, from among ambulatory employees and friends. In the few instances where patients were selected from the medical wards a careful study had shown no cardiovascular disease or symptom. Systolic hypertension of 150 to 160 mm. Hg with a diastolic pressure of 90 mm. or less was not considered grounds for exclusion from the study, but only two patients had such elevations. No patients were included who had abnormal electrocardiograms, enlarged cardiac silhouettes, pulmonary infiltrations, obstructive emphysema, pleural disease, anemia or deformities of the thoracic cage.

The method for recording a simultaneous three-plane ballistocardiogram together with lead II of the electrocardiogram has been described in detail elsewhere.[7] Briefly, longitudinal motion was sensed by the Dock electromagnetic unit on the shins with a 20 microfarad condenser in a circuit with 3,000 ohms resistance. With this pick-up, 1 mv. equals 0.055 mm. displacement at 2 cycles per second, and 0.050 mm. at 10 cycles per second. The condenser partially integrates the velocity signal, reducing fast waves due to tremor and showing less respiratory undulations, when the patient is breathing tidally than would pure displacement curves.[1] Lateral and dorsoventral motion were sensed from the thorax, by a system of platforms mounted on stiff springs. The signals for each of these movements were picked up by appropriately placed coils and magnets, with 30 microfarad condensers in the circuits. The sensitivity of the lateral unit was adjusted when turned at right angles and recording head-foot motion, giving curves similar in form and size to those simultaneously recorded from the shins. Both lateral and dorsal systems had an output of 1.2 mv. when a force of 50,000 dynes was applied suddenly. A Sanborn 4-channel Polyviso was employed to inscribe the three ballistocardiograms, and either lead II of the electrocardiogram or the heart sounds, with sensitivity of 10 millimeters per millivolt.

All patients were ambulatory and no attempt was made to have them in a truly basal state at the time of the study. However, records were never taken less than two hours after a meal, less than an hour after smoking a cigarette, or after any physical of emotional stress. The subjects lay on the recording table until pulse and blood pressure were constant. A 12-lead electrocardiogram was recorded, and then the three-plane ballistocardiogram. In addition 24 of the 38 volunteers in the younger age group were subjected to 20 trips over the Master steps, and the ballistocardiogram was observed promptly, following exertion. Often three to five minutes would elapse before a satisfactory record could be made. Exercise was not done in the older age group. Where increase in posterior-anterior diameter of the chest was significant, fluoroscopy was performed. Patients with hyperilluminated lung fields, diminished movement of the thoracic cage, or poor diaphragmatic motion were eliminated from the study. The position of the heart and aorta in all patients was also studied either fluoroscopically or radiographically, or by both methods.

Results

The data for both groups are given in table 1.

Findings in Subjects from Twenty to Twenty-nine Years of Age

Longitudinal Ballistocardiogram

There were no abnormalities of form or amplitude of the longitudinal ballistocardiogram in this group. The amplitudes for IJ were averaged in inspiration and expiration for each sex separately. For men, the range in inspiration (IJ_I) was 1.3 to 3.8 mv., and in expiration (IJ_E) was 1.0 to 3.4 mv. The mean IJ_I was 2.5 mv., and mean IJ_E was 1.9 mv. For women, the

TABLE 1—*Three-Plane Ballistocardiography**

	20–29 Years		50–75 Years	
	Males	Females	Males	Females
No. Cases	23	15	17	15
Mean Age (Years)	25.5	24.4	59.8	57.0
Longitudinal BCG				
Abnormals	0	0	Grade I 8 (47.1%) Grade II 3 (17.6%) Grade IV 1 (5.9%)	Grade I 6 (40%) Grade II 1 (6.7%) Grade III 1 (6.7%)
IJ Amplitude				
Range (mv.)	IJ_I = 1.3–3.8 IJ_E = 1.0–3.4	IJ_I = 1.1–3.0 IJ_E = 0.9–2.3	IJ_I = 1.1–2.8 IJ_E = 0.4–1.8	IJ_I = 0.8–1.6 IJ_E = 0.6–1.3
Mean (mv.)	IJ_I = 2.5 IJ_E = 1.9	IJ_I = 1.9 IJ_E = 1.5	IJ_I = 2.0 IJ_E = 0.8	IJ_I = 1.3 IJ_E = 0.8
Lateral BCG				
IJ Amplitude				
Range (mv.)	IJ_I = 0.6–4.1 IJ_E = 0.6–4.3	IJ_I = 0.2–2.3 IJ_E = 0.2–2.5	IJ_I = 0.5–4.6 IJ_E = 0.5–4.3	IJ_I = 0.6–3.0 IJ_E = 0.6–7.7
Mean (mv.)	IJ_I = 1.5 IJ_E = 1.8	IJ_I = 1.2 IJ_E = 1.3	IJ_I = 2.3 IJ_E = 2.3	IJ_I = 1.6 IJ_E = 1.6
S.D. (mv.)	IJ_I = 0.9 IJ_E = 0.9	IJ_I = 0.55 IJ_E = 0.59	IJ_I = 1.1 IJ_E = 1.0	IJ_I = 0.7 IJ_E = 0.7
Q-BCG (sec.)				
	Mean Range	*Mean Range*	*Mean Range*	*Mean Range*
Q-H	0.12 (0.10–0.14)	0.11 (0.08–0.12)	0.12 (0.10–0.14)	0.12 (0.10–0.14)
Q-I	0.20 (0.16–0.24)	0.19 (0.16–0.20)	0.20 (0.18–0.20)	0.19 (0.16–0.20)
Q-J	0.29 (0.26–0.34)	0.26 (0.22–0.30)	0.28 (0.24–0.30)	0.27 (0.24–0.28)
Q-K	0.39 (0.36–0.42)	0.35 (0.32–0.38)	0.36 (0.34–0.38)	0.34 (0.30–0.36)
H-K	0.26 (0.22–0.30)	0.24 (0.22–0.30)	0.23 (0.22–0.26)	0.23 (0.20–0.26)
Dorsoventral BCG				
IJ Amplitude				
Range (mv.)	IJ_I = 0.9–1.8 IJ_E = 0.3–1.6	IJ_I = 0.3–1.0 IJ_E = 0.3–0.8	IJ_I = 0.6–1.7 IJ_E = 0.4–1.5	IJ_I = 0.7–1.4 IJ_E = 0.2–1.0
Mean (mv.)	IJ_I = 1.1 IJ_E = 0.9	IJ_I = 0.7 IJ_E = 0.6	IJ_I = 1.1 IJ_E = 0.8	IJ_I = 0.7 IJ_E = 0.6

* The range and mean amplitude for IJ in three planes for each age group by sex, in inspiration and expiration. For lateral IJ the standard deviations are included. Note that in young subjects, mean lateral IJ in expiration (IJ_E) is greater than IJ in inspiration (IJ_I) but in the elderly people, they are the same. It is significant that mean IJ in expiration (IJ_E) declines 58 per cent with age in men, when calculated from the longitudinal ballistocardiogram alone, but that the decline is only 15 per cent when mean IJ in expiration for each group is summated in three planes.

range of IJ in inspiration was 1.1 to 3.0 mv., and in expiration was 0.9 to 2.3 mv. Mean IJ_I and IJ_E was 1.9 mv. and 1.5 mv., respectively. The overall average is equivalent to a displacement of 87 micra or 0.0035 inches.

The intrinsic difficulties in calibrating direct-body ballistocardiographs have been outlined by Bixby.[1] In the only comparable study with a calibrated electromagnetic ballistocardiograph, the mean IJ displacement for a group of 50 normal flight personnel of both sexes between the ages of 30 and 40 years was 0.0023 inches.[15] The mean IJ for both sexes in the current study averaged 50 per cent greater. Some of the discrepancy is due to more accurate calibration of Smith's instrument, some to the fact that his subjects were a decade older and were studied when closer to the basal state than those in this study. The two latter factors could account for lower values of displacement.

The "Ra" ratio, $\left(\frac{IJ_E}{IJ_I} \times 100\right)$ was below the mean value of 72 for this age group as derived by Scarborough,[13] in only five instances, and in no case was it below 60.

Lateral Ballistocardiogram

In this study, our laboratory used the conventions first suggested by the Committee on Ballistocardiographic Terminology.[20] An upward deflection represents leftward motion, and a downward deflection indicates rightward motion. The lateral IJ in normal subjects moves from left to right, as would be expected from the rightward and headward orientation of the long axis of the heart from apex to base, and from the headward direction of IJ.

Easily measurable, lateral HIJK complexes were recorded in this group with only one exception. The form of the complexes on superficial inspection simulated the longitudinally inscribed ballistocardiogram. However, the lateral I wave is not infrequently as much as 0.02 second later than the head-foot I. The dominant stroke of the lateral complex is the leftward I wave rather than the rightward J. The leftward K is relatively small, compared to that on the head-foot trace.

Typical and average lateral ballistocardiograms are shown in figures 1 and 3*A*. The head-foot trace recorded simultaneously shows the relationships to the longitudinal plane, and lead II gives the relation to the electrical forces. Where ballistic form is abnormal, the electrocardiogram is essential for accurate identification of IJ in any plane.

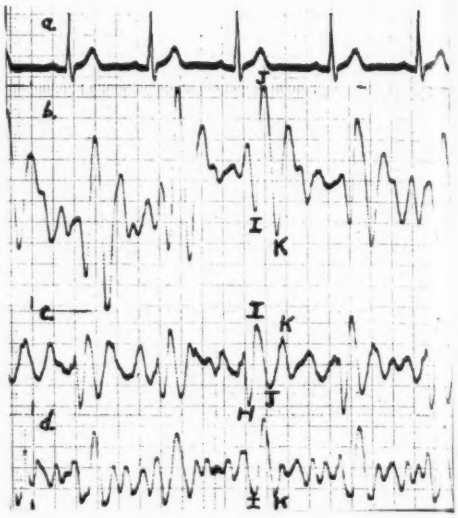


FIG. 1. Three-plane ballistocardiogram of a 26 year old man. (a) Lead II of electrocardiogram. In all these ballistocardiograms (b, c, d) upward means headward, leftward or backward motion of the thorax. (b) Longitudinal. The baseline undulation is at its summit in inspiration and declines with expiration. (c) Lateral. Note deep H wave, leftward I and rightward J. Lateral IJ is maximal in expiration, when longitudinal IJ is smallest. (d) Dorsoventral. In this trace IJ and the JK to IJ ratio are larger than the average for this plane. The form of the complexes is very similar to that of the longitudinal ballistocardiogram.

Usually a sharp leftward, initial deflection precedes the rightward H wave. This initial component is usually small, rarely exceeding 0.5 mv. and often varies from complex to complex and with respiration. At times it is absent and only a rightward H wave is seen. A true G deflection, of ventricular origin, has been observed previously in our lateral traces in the presence of complete heart block or atrial fibrillation. Where A-V conduction is normal, the initial wave (G or atrial i) is probably due in large part to the footward and leftward movement of the body as blood enters the

ventricles under the impact of atrial systole. Where A-V conduction is abnormal and atrial systole does not precede the Q wave of the electrocardiogram, G may be due to movement of the ventricle in the mediastinum as contraction sets in, but before the intraventricular pressure exceeds that in the atriums.[5] The H wave is always represented in the lateral trace as a distinct rightward movement and is, at times, even larger than the J wave in lateral planes. In this laboratory, the H wave is ascribed to headward and rightward impact on the atrial-ventricular septum at the peak of isometric contraction.

In A-V block the atrial j wave occurs 0.24 to 0.30 second after the onset of the atrial P wave, and the headward component may be due in part to rapid return of blood to the right auricle from the inferior vena cava. But the relatively much larger rightward atrial j in lateral traces can not be due to this force, since the vein has a vertical path. It seems more probable that the reflux of blood from the ventricles, as atrial pressure falls, is the cause of both lateral and vertical j waves. With normal A-V conduction j is superimposed on H.

The normal lateral I is always leftward and its peak in about half the cases occurs 0.02 second later than that of the longitudinal I. The delay does not represent an instrumental artifact but may be related to differences in compliance of the mediastinum from one plane to another, or to true differences in peak of application of force in the two planes. The time interval from nadir of H to peak of I is most commonly 0.08 second but ranges from 0.06 to 0.10 second and would appear to be unrelated to sex or body size. The lateral HI stroke is often of greater amplitude than that of IJ.

The J wave is directed rightward, as well as headward and backward. Because I is a large wave, the IJ sweep in 42 per cent of these subjects was the largest lateral wave, in 11 per cent it equalled HI, while in 4 per cent HI was larger. However in the women under 30 years of age, IJ was larger than HI in only 21 per cent, while it was larger than HI in 55 per cent of the young men.

Distribution curves for the amplitude of the lateral IJ waves are shown in figure 2, where

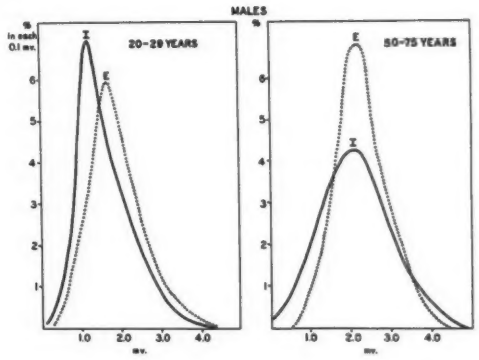


FIG. 2. Distribution curves for the amplitude of IJ waves in the lateral ballistocardiograms of young and elderly men. Solid lines for the smallest wave, during inspiration and dotted lines for the largest wave, during expiration for typical respiratory cycle of each subject. The smoothed curves show per cent of subjects in each 0.1 mv. range. Young men have smaller waves, but a larger respiratory variation, than older ones.

the per cent of subjects is plotted against IJ amplitude in 0.1-mv. units in the manner of Soldati.[16] The mode for the inspiratory IJ is 1.2 mv. in young men, the mode for expiratory IJ is 1.6 mv. In men the range is 0.6 to 4.3 mv. in inspiration, for women 0.2 to 2.5 mv. The mean inspiratory IJ for men was 1.5 mv. and mean expiratory IJ was 1.8 mv. This reflects the tendency in this group for lateral IJ amplitudes to *increase* about 20 per cent with expiration.

Except for a few unusually high values among men, the figures are quite homogeneous. One standard deviation each side of the mean embraces all but two of the IJ amplitudes in inspiration, but excludes five of these amplitudes in expiration. For women, mean inspiratory and expiratory IJ's were 1.2 mv., and 1.3 mv., respectively. No unusually high values were found in this group, but there were two very low ones. Although the mean IJ for women was less than for men, especially in expiration, the difference is not as great as the sex difference for the head-foot IJ.

Attention was given to the relation of body size and contour and of electric and radiographic position of the heart to IJ amplitude. Body contour did not appear to be a significant

factor but height and weight probably are related. Thus, the smallest lateral IJ's (0.2, 0.4 and 0.6 mv. in inspiration) occurred in women who were 5 feet 4 inches or less in height and who weighed between 112 and 120 pounds. Tall women and men (5 feet 8½ inches, 150 pounds) had average sized IJ strokes. The largest lateral IJ waves (3.8 to 4.1 mv. in inspiration) were found in heavy-set men of about average height with a tendency to obesity, but some subjects with similar build had average deflections. Electrically the heart usually was vertical or semivertical, and anatomically it was most commonly intermediate. No significant relation of these axes with IJ could be demonstrated.

The duration of IJ is usually between 0.08 to 0.10 second, and is on the average slightly longer than for the HI duration. In four instances in which IJ duration was only 0.06, second, the patients were women, 5 feet 5 inches or less, weighing 125 pounds or less.

The lateral JK, a right to left movement, is always the smallest deflection of the systolic complex. It is most commonly 0.10 second in duration when the K peak is sharp. Often, however, this peak is blunt or indistinct or, less commonly, merges into small oscillations of the base line. Since the K deflection is believed to originate in the descending portion of the aorta, an almost purely longitudinal structure, one would not expect a significant lateral K wave.

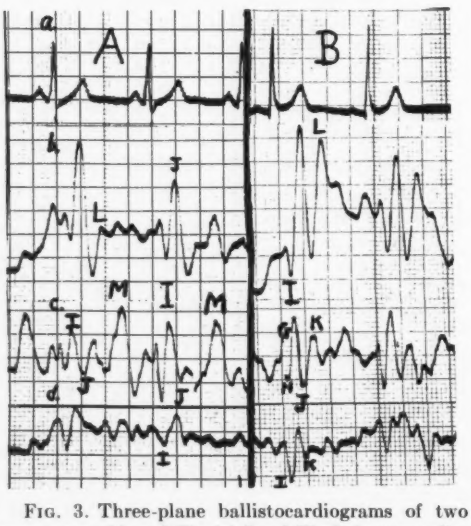


FIG. 3. Three-plane ballistocardiograms of two young men (*A* and *B*). (a) Lead II of electrocardiogram. (b) Head-foot trace; note very tall L wave with short K in *B*; the reverse, as in *A*, is more often noted. First IJ (end of inspiration) is larger than second, in expiration. (c) Left-right traces; IJ increasing during expiration, especially in *A*; initial *G* largest in *B*; diastolic M, largest in *A*, where it exceeds the largest IJ. (d) Back-front traces; resemble the head-foot traces, but much smaller.

Diastolic waves ranging from 0.7 to 2.0 mv. in amplitude were common. Occasionally a diastolic deflection, M, was the predominant wave of the lateral ballistocardiogram, (fig. 3*A*). Its longest slope was invariably leftward, although it overlaps in time the headward L or N wave, more commonly the former. Actually, it is inscribed after a short rightward L, and so it may be considered as the lateral M wave. Diastolic waves are now regarded as real forces, rather than as postsystolic oscillations. The leftward deflections in lateral ballistocardiograms would suggest that M is due, in this plane at least, to the ventricular diastolic inflow. No relation of large diastolic waves to physiologic third heart sounds was apparent in these young adults.

Of some interest was the occasional appearance in lateral traces of rapid deflections, coincident with the end of the electrocardiographic T wave. These presumably are due to the impact causing the second heart sound. Such waves have previously been reported in ballistocardiograms taken directly from the chest.[8]

Q-Ballistocardiogram Intervals. Time intervals from Q to H, I, J, K, and H-K time were measured, wherever reasonable accuracy was assured by the preciseness of wave form. These intervals are all somewhat shorter for women and the difference increases with the later systolic deflections. Thus mean Q-H was 0.10 and 0.11 second for men and women, respectively, and mean Q-I was 0.20 and 0.19, but for Q-J, the relative values were 0.29 and 0.26, and for Q-K 0.39 and 0.35 second. Mean H-K for men was 0.26, for women 0.24 second. These findings show the same trend as Scarborough's figures.[14] Whereas difference in sex in his study was not significant for Q-H and

Q-J times, it was slight but significant for Q-J and Q-K. This author was inclined to relate the difference to body size, especially weight. The present figures tend to support such a view, and the shortest Q-K for women also appeared in the smallest and lightest subjects. Relatively heavier women, regardless of height had Q-K times comparable to men of medium stature and weight. The longest Q-K interval (0.40 second) appeared in heavy men, regardless of height.

Effect of Exercise. In roughly two-thirds of the cases, the effect of exercise on the lateral complex was studied by having the subjects take 20 trips over the Masters steps. Respiratory artifacts often made it impossible to quantitate the immediate effects of exercise. When the records became legible the head-foot complexes usually showed IJ's of greater amplitude than the control trace, but sometimes, at fast heart rates, they were unchanged. In either event the lateral I-J complexes became significantly reduced in size, at times markedly so and HI became more prominent. Usually, this was relative to the reduction in IJ, but occasionally an actual increase in the depth of the H wave was noted. The change in size of the diastolic waves after exercise was variable, but increases were more frequent than decreases.

Dorsoventral Ballistocardiogram

The dorsoventral HIJK is usually of small amplitude, but when it is large and neatly inscribed, it has a form very similar to the longitudinal ballistocardiogram (fig. 1). By the accepted convention, ventral movements are downward, and dorsal movements upward on the recording paper.

After a short, often blunt, dorsally directed H wave, the I deflection is written in a ventral direction, the J wave moves sharply backward and K returns ventrally. Even when the dorsoventral ballistocardiogram is large and distinct, the K wave is never deeper than I, although it may be of equal amplitude. The orientation of the dorsoventral IJ (IJ_{DV}) is a consequence of the fact that the apex of the heart is more ventrally located than the base and that during early systole, when the I wave is inscribed, the heart rotates clockwise and anteriorly and is thrust toward the chest wall, leftward and frontward, by the recoil from early ejection. The impact on the aortic arch and the pulmonary artery's bifurcation thrusts the body headward, backward and rightward, causing the J wave.

In most cases, though IJ_{DV} is the dominant deflection, it is nevertheless of small amplitude and may be slurred or notched. Notching is more likely to occur in expiration, but is not limited to this phase of the respiratory cycle. The JK stroke is even more variable. It often is no more than 50 per cent of the dorsoventral IJ in amplitude, and its terminal portion may be represented merely by an undulation of the isoelectric line (fig. 3*B*).

The range of IJ in dorsoventral ballistocardiograms in males was from 0.9 to 1.8 mv. in inspiration, and from 0.3 to 1.6 mv. in expiration; for females, the range was from 0.3 to 1.0 mv. in inspiration, and 0.3 to 0.8 mv. in expiration. The mean inspiratory IJ for men was 1.1 mv. and mean expiration IJ was 0.9 mv. For females these values were 0.73 mv. and 0.59 mv., respectively. It is to be noted that for men the scatter is considerable and two-thirds of the inspiratory IJ values are below the mean. For women, the grouping is better and mean values are smaller. The dorsoventral IJ, like the head-foot IJ but opposite to the lateral IJ, is greater in inspiration than in expiration. It usually is larger after exercise.

Q-ballistocardiogram intervals are shorter in this plane, but H-K time agrees almost always within 0.02 second with H-K for longitudinal and lateral ballistocardiograms. The discrepancy in Q-ballistocardiogram intervals among the various planes is a result of the earlier onset of ballistic activity dorsoventrally. Whereas IJ of the lateral ballistocardiogram may be 0.02 second later than the head-foot IJ (IJ_{HF}), dorsoventral IJ is from 0.02 to 0.06 second earlier than IJ of the head-foot ballistocardiogram, usually 0.04 second. The reason for this is not clear, but it is obvious that while the body must be set into motion and slide some distance before head-foot or lateral force fully expresses itself, whether recorded directly or from a platform, dorsoventral force is applied directly to the platform on which the body lies.

Findings in Subjects Fifty to Seventy-five Years of Age

Longitudinal Ballistocardiogram (29 per cent)

In this age group only 29 per cent of the head-foot ballistocardiograms in men would be called normal, if the records were graded according to the system originally proposed by Brown.[4] By these criteria 47 per cent were grade I, and the remaining 24 per cent represented grade II–IV abnormalities. The women had a higher percentage of normal traces, 47 per cent, but some of them were of very small amplitude. Forty per cent were classified grade I, and only 13 per cent were grade II and III. No grade IV records occurred in women. The most common abnormalities were absence of the I and J waves, either of very small amplitude or notched during expiration. Relatively large H, small I and J waves formed an occasional complex which Starr[17] calls "early M" because the tracing in early systole looks like that letter.

When IJ was consistent and measurable, mean IJ of inspiration was 1.3 mv., and IJ of expiration was 0.84 mv. indicating smaller mean amplitudes, but less phasic variation, thereby accounting for the smaller number of abnormal traces in older women. These figures, in general, are consistent with previous studies showing high percentages of abnormal longitudinal ballistocardiograms above the age of fifty in males.[6, 13]

Lateral Ballistocardiograms

The form of the lateral ballistocardiogram in this group is similar to that in younger normals. The distribution curve in figure 2 indicates that in older men the mode for IJ of inspiration and for IJ of expiration are both about 2.0 mv. Mean IJ of inspiration increases with age, especially in men, but the tendency for expiratory IJ to be larger than inspiratory IJ in this plane is not as consistent in this group as with the younger people. The mean lateral IJ of inspiration for men was 2.29 mv., and for expiration was 2.34 mv.; for women the respective values were 1.62 and 1.61 mv. The range of amplitudes for men was considerable, inspiratory IJ varying from 0.5 to 4.6 mv., and expiratory IJ varying from 0.5 to 4.3 mv. For women the range was less, being from 0.6 to 3.0 mv. for inspiratory IJ, and from 0.6 to 2.7 mv. for expiratory IJ.

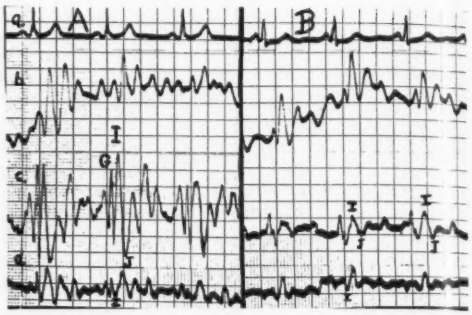


FIG. 4. Three-plane ballistocardiograms from two men over 50 years old (*A* and *B*), showing lateral traces (c) at the extremes of normal variation in size, and systolic complexes decreasing during expiration in all three planes.

Striking reciprocal relations of the lateral to the longitudinal ballistocardiogram were noted. When the head-foot trace is normal, the lateral amplitudes usually vary reciprocally with the head-foot amplitudes. Although elderly subjects may have quite large waves synchronously in two planes or even in all three planes, it is more common for lateral deflections to be large when longitudinal ones are small (fig. 4*A*) and for this component to be small when head-foot is large (fig. 4*B*). This may be apparent in any individual during each respiratory cycle, when the IJ waves in one plane become large while the other plane shows a decrease. In longitudinal traces with otherwise good form and normal respiratory variation but which exhibit the short I that Starr has ascribed to aging,[18] an I of good amplitude often is present in the lateral projection.

Subjects with grade I longitudinal traces offered the best opportunities for such comparison with lateral traces. In about 85 per cent of the 14 patients of both sexes with such a head-foot classification, the lateral ballistocardiograms fell into two categories, both of which may be considered to be compatible with normal action of the ventricles. One type of record, representing the more common situation, displays lateral IJ deflections of good

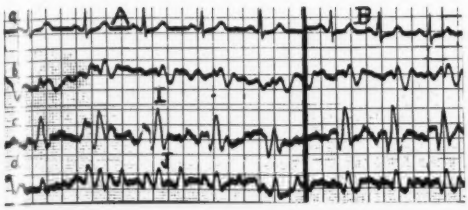


FIG. 5. From a normal woman, age 65. (*A*) normal breathing; (*B*) held inspiration. The head-foot trace (b) could be classified as grade II or even III, because of its respiratory variation, small amplitude, and deep K wave. The dorsoventral (d) has larger J waves, and the lateral (c) shows large HI complexes, smaller during expiration.

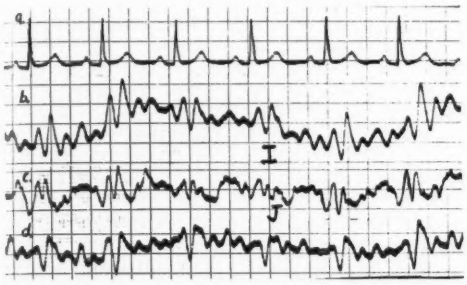


FIG. 6. From a normal man, age 50. The third and fourth beats, during expiration, show greater decrease in size of lateral systolic waves (c) than in head-foot (b) or dorsoventral waves (d).

amplitude and constant form, varying little with respiration, but tending like the head-foot IJ, to decrease during expiration (figs. 4 and 5). In these patients the ratio, $IJ_{Expiration} \times 100$ was always well within normal limits when the accepted values for $IJ_{Inspiration}$ head-foot IJ variation are applied to this stroke in the lateral plane. More rarely, lateral systolic complexes were more than halved during expiration, and changed more than did head-foot IJ complexes (fig. 6).

In a second category, much less frequently seen in normals, aged 50 to 65, but not rare in hypertensives or senile males, the lateral trace shows a respiratory swing in amplitude which causes the smallest IJ to be less than half the largest in each respiratory cycle. But whereas in cases where the H-F varies, the ratio $IJ_{Expiratory}/IJ_{Inspiratory}$ is always less than 1, and in grade I or II records is less than 0.5, in these laterals with large variation this ratio is over 2.0. The respiratory lateral IJ becomes abnormally small during inspiration, just as the corresponding head-foot IJ becomes large. It is obvious that in these cases, total systolic force applied to the body is relatively constant during the respiratory cycle, but the vector of its application swings through a wide arc. In this group, too, belong cases with chaotic complexes in the head-foot tracing but with large systolic lateral complexes which are smaller during inspiration than expiration (fig. 7).

In two instances (14.5 per cent of the grade I longitudinal traces), the lateral deflections were small or varied excessively in form and amplitude at the same time in the respiratory cycle, when the longitudinal complexes were small or notched. Figure 6 is an example of such a case. Note that the IJ amplitude diminishes concomitantly in all three planes.

Four grade II head-foot traces were noted. Three of these had constant, large lateral IJ deflections and in two, the lateral amplitudes varied reciprocally with the head-foot IJ. In one instance, the IJ of the lateral ballistocardiogram was small and did not improve in form or amplitude in a reciprocal manner as head-foot complexes deteriorated.

Only two ballistocardiograms were classified grade III or IV. In both instances, the form and amplitude of lateral IJ were clearly normal and in one instance the IJ of the lateral ballistocardiogram was among the largest recorded (fig. 7).

Diastolic waves were seen in lateral ballistocardiograms in this group, as in the younger

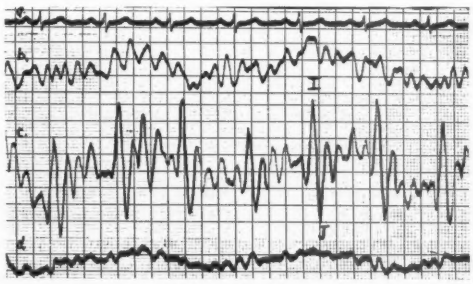


FIG. 7. From a healthy man, 60 years old. The head-foot (b) and front-back (d) traces are chaotic (grade IV), while the lateral systolic waves are huge, although the complexes decrease at the onset of inspiration (first, fourth and seventh beats).

subjects. Their frequency, amplitude and orientation were not significantly different from the previous characterization given of diastolic ballistic waves in that group.

Q-BCG intervals and H-K time. The tendency for Q-J, Q-K and H-K to be longer in men than in women was not as clear for this group as in the younger subjects. This may be due in part to the more closely comparable height and weight in the older subjects of both sexes. For males, Q-H was 0.12, Q-I, 0.20, Q-J, 0.28, Q-K, 0.36 and H-K, 0.24 second. For females, Q-H was 0.12, Q-I, 0.19, Q-J, 0.27, Q-K, 0.34 and H-K, 0.22 second. As seen in table 1, there is no increase in Q-BCG time with age.

The Dorsoventral Ballistocardiogram

Motion in the dorsoventral plane in elderly patients shows no significant change when compared with the scatter for the younger age group. In contrast to lateral IJ there is no tendency for older people to have larger dorsoventral IJ, and the mean values for men ($IJ_{Inspiratory}$ 1.08 mv., $IJ_{Expiratory}$ 0.76 mv.) and women ($IJ_{Inspiratory}$ 0.72 mv., $IJ_{Expiratory}$ 0.54 mv.) were very similar to those of the young adults.

Although the dorsoventral amplitudes were generally small and the complexes indistinct, it was noted that for men there is a wide spread from the mean value. In some older men, normal or with healed infarcts, but usually with relatively large anterior-posterior diameters of the chest, IJ in lateral and IJ in head-foot ballistocardiograms may be abnormally small or deformed, whereas a prominent and well-formed dorsoventral complex may be inscribed (fig. 8). In these instances, abnormalities in other planes may be ascribable to change in the axis of force and may be less significant evidence of poor myocardial function.

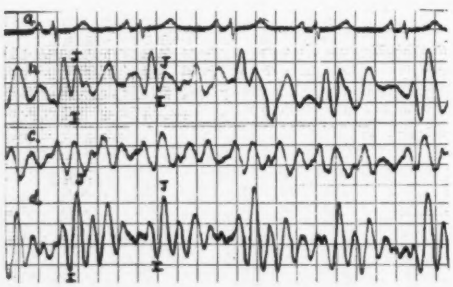


FIG. 8. From a man 54, asymptomatic but convalescent from a minor episode of cardiac infarction. The head-foot trace shows large H and small notched J waves, but in the dorsoventral trace IJ is unusually tall and appears normal. This subject had a very deep chest, as have others, where dorsoventral IJ is large.

As in the younger group H-K time in the dorsoventral plane usually fell within 0.02 second of the corresponding H-K for the other planes. The tendency, for I in dorsoventral ballistocardiogram to be inscribed as much as 0.04 second earlier than I in the head-foot ballistocardiogram, persists in this group.

DISCUSSION

In this study, the lateral IJ wave of young adults seemed almost equal in force to the head-foot systolic wave and the chief difference was that the J wave is larger in the longitudinal and the I wave in the lateral plane. Also, while the head-foot waves normally are largest during the inspiratory phase, the lateral waves are largest during expiration. It should be noted that with the use of blocks on each side in order to obtain good transmission of lateral forces and to prevent the thorax from rolling on the platform, the lateral systolic waves are much closer in size to the head-foot waves than had been suggested by earlier studies in this laboratory and elsewhere. There is little doubt that the system, described here, transmits to the table a higher percentage of lateral than of longitudinal force. Effective vertical blocks at the shoulders and pubis probably would be needed to correct this instrumental difference. Study of the anatomy of the outflow tracts in angiocardiograms indicates that the right ventricle can exert very little lateral force and that the left ventricle normally has its axis of ejection close to 45 degrees to the right of the vertical axis of the spine. Therefore, the normal lateral force probably varies from one-third to two-thirds, the longitudinal thrust during recoil from ejection (I wave) and from one-fifth to one-third during impact on the arch or bifurcation of the great arteries. Quantitative photoelectric records from the base of the sternum show about three to five times more longitudinal than lateral displacement in nor-

nal young subjects, but since the ribcage is more easily moved longitudinally than laterally, this probably minimizes the effect of the lateral thrust.

Even with our present method, which tends to exaggerate the relative force of the lateral and front-back thrusts, as compared with longitudinal ones, it is apparent that most young adults and many elderly people have relatively large head-foot ballistocardiographic waves and relatively small dorsoventral ones. The lateral waves, which average somewhat smaller than head-foot waves in young adults, become relatively large, however, in the elderly subjects. Relatively large back-front waves are encountered rarely and only in deep-chested older subjects with small head-foot waves.

Age causes a much greater decrease in the head-foot waves inscribed during expiration than in those during inspiration. In this study, the smallest IJ in the cycle was 42 per cent as large in those over 50, as compared with the smallest waves in those 20 to 30 years old. A comparison of the lateral waves inscribed synchronously with these small beats, showed that they were 22 per cent larger in the old group as compared with the younger one. In the younger group, the lateral waves average a 30 per cent increase during expiration than during inspiration, when the smallest head-foot waves are inscribed. In older people, the average lateral IJ is larger than in younger ones, but its change during the respiratory cycle is less. It may *decrease* in amplitude during the expiratory phase in older subjects, but very rarely does so in the younger ones.

The causes for the change in vectors with age are not fully understood, but the cause for the increase in the lateral waves during expiration is apparent. The rise of the diaphragm results in upward motion of the apex and the axis of ejection of the left ventricle becomes more transverse at the same time that the stroke volume increases, due to increased filling as blood is forced out of the pulmonary veins by decrease in lung volume. In young people, the diaphragm moves more than in elderly or emphysematous ones, so that one would expect a larger respiratory change in axis in young people than in the aged and also a greater change in men than in women, since costal breathing is relatively great, diaphragmatic breathing less in women.

The most important factor in the increase in lateral waves in older men undoubtedly is the tortuosity of the aorta.[7] As this vessel becomes longer and bows farther to the right in its ascending portion, the axis of ejection of the left ventricle becomes more transverse. There is a general, but not a consistent, relationship between the tortuosity of the ascending parts of the aorta and large lateral IJ waves; the exceptions are usually in subjects with large IJ waves, but no striking prominence of the ascending aorta. Although a significant number of individuals who have predominantly laterally directed ballistocardiograms do have dilated, tortuous aortas, such a vector change may be present in individuals whose ascending aortas on radiographic examination do not appear to be different from those of young people. Conversely, the arch is dilated in some patients whose lateral complexes are very small. However, since the initial portion of this vessel is concealed in the mediastinal shadow, angiocardiograms are needed to show whether the angle of ejection from the ventricle lies transversely.

Physiologic considerations; thus far unstudied, may also have a role in the genesis of a large lateral IJ wave. The position of the A-V atrial-ventricular septum at the time the IJ stroke is inscribed may play a role in determining the size of the HIJ complex, for with early ectopic beats the head-foot IJ is often much smaller than in the normal beat, while the lateral HIJ, with slightly shifted time of occurrence of its peaks, is as large as in the normal cycles.

There may also be some effect of age on the relative velocity of ejection from each ventricle. A delay in aortic ejection, relative to pulmonic ejection, would cause recoil from left ventricular ejection to coincide with impact on the pulmonary artery bifurcation and explain a large I wave laterally, when the head-foot I wave is absent. Study of the three-plane ballistocardiogram in bundle branch block might be profitable, although the failure of Samet[11] to observe consistent delay in ejection from the

ventricle with "delayed activation" makes timing of ejection essential in each case.

So far, as the effect of age on the force of systolic thrust is concerned, the mean head-foot IJ wave decrease is very much greater than that of the sum of the thrusts in three planes. This sum, for the beat with the largest head-foot IJ waves is about as large in our subjects over 50 as in those under 30, while the sum of forces during the beats with the smallest head-foot IJ was only 15 per cent less in the elderly subjects than in the young ones, although in the head-foot IJ for these beats, the mean decrease in size was 58 per cent.

At the present time, it seems justifiable to consider as normal all tracings in which the form of the complexes is not bizarre and the ratio $IJ_{Head\text{-}Foot} + IJ_{Lateral}$ (expiratory) $\times$ 100/ $IJ_{Head\text{-}Foot} + IJ_{Lateral}$ (inspiratory) is over 60. This would give less than 10 per cent of abnormal traces in our group of normals over 50 years of age, while applying deLalla and Brown's original system of grading to the head-foot traces, with a ratio below 50 considered abnormal, 64 per cent of our subjects had abnormal head-foot traces.

The percentage of presumably normal tracings rises sharply when three-plane rather than head-foot traces are used in the study of normal people past the fifth decade, but there is also a rise in the per cent of normal tracings, obtained from those with healed infarction of the heart. Since the normal three-plane traces are most often found in patients who are asymptomatic after recovery, this method of classification gives better agreement with clinical findings, as well as far fewer false positives in elderly normals, than does any classification based on head-foot tracings alone. However, one may well regard as abnormal traces in which there are extreme even though reciprocal, changes in the lateral complexes. The case shown by Dock[7] (fig. 4) gives a ratio over 100, but shows a decrease in lateral IJ waves during inspiration which suggests a paradoxic pulse, since it is much greater than anything seen in records from normals. Even in three-plane ballistocardiography, one must look at the traces and not depend on measured amplitudes or ratios alone.

Summary

(1) Simultaneous three-plane ballistocardiograms have been inscribed in a group of 38 men and women under 30 years, and in another group of 32 people over 50 years. History, complete physical examination, chest roentgenograms and 12-lead electrocardiograms showed no evidence of cardiac or pulmonary disease in any of these subjects.

(2) The sensing systems used gave approximately equal signals to equal forces applied to the thorax in three planes.

(3) The normal variations in form and size of the ballistic waves are described and the range and mean values of the main systolic wave, IJ, are given for the two sexes in each age group.

(4) The IJ wave is directed headward, rightward and backward; its peaks occur earlier in the backward, and later in the rightward direction than in the classic head-foot trace.

(5) The IJ wave decreases more during expiration in the head-foot than in the dorsoventral tracing, in young people. An expiratory decrease, in head-foot IJ, is marked in older subjects, but in the dorsal wave is about the same in the elderly as in the young and is greater in men than in women in both groups.

(6) The lateral IJ increases during expiration and with age. The expiratory increase is more marked in young men, and is barely evident in many older subjects. However, some older normal subjects, with very great expiratory decreases in longitudinal IJ waves, have striking increases in the lateral waves inscribed by the same heart beats.

(7) It would appear that in young individuals, the ballistic systolic forces are predominantly longitudinal, but with age, the force vector changes and in middle aged or elderly individuals, it may have an almost purely lateral representation.

(8) In three-plane ballistocardiograms with small amplitude or abnormal head-foot tracings in which lateral IJ is uniformally large or increases during the part of the respiratory cycle when head-foot IJ becomes abnormally small, changes in direction of ejection rather than in cardiac force are probably determining

the character of the record. The causes of these changes are unsettled, but elevation of the diaphragm with expiration, a more transverse position of the heart and greater aortic tortuosity in the aged deserve study. Other factors, such as change in the time interval between the onset of the pulmonary and aortic pulse waves, may also prove to be significant in causing this sign of aging.

(9) The ratio [$IJ_{Head\text{-}Foot}$ + $IJ_{Lateral}$ (Expiratory)/$IJ_{Head\text{-}Foot}$ + $IJ_{Lateral}$ (Inspiratory)] × 100 has been introduced for the purpose of grading three-plane ballistocardiograms. In 38 subjects, 20 to 29 years old, the mean value for this ratio is 91 and the lowest is 81. In only 3 of the 32 subjects over 50 years of age was this ratio below 60, whereas in 20 of these subjects the ratio [$IJ_{Head\text{-}Foot}$ (Expiratory)/$IJ_{Head\text{-}Foot}$ (Inspiratory)] × 100 was below 50 and would therefore be considered abnormal according to the Brown convention.

(10) Any conclusions as to force of ventricular systole in subjects over 40 years old must be fallacious if based on classic head-foot ballistic waves alone, for the vector of force changes more than the total force of systole in older subjects, especially in males. Study of the total ballistic forces is not adequate unless body motion is recorded in at least the lateral and head-foot planes. Ideally, it should be registered in all three planes, with the lateral and dorsoventral force recorded from the thorax.

Acknowledgment

The kindness of Dr. Herman Ruskin in recording several of the ballistocardiograms used in this study is gratefully acknowledged.

Summario in Interlingua

Le motiones del thorace e del tibia esseva registrate per medio de un technica que resulta in undas de approximativemente le mesme dimensiones quando un fortia identic es applicate al thorace in le un o in le altere del tres planos. Le registrationes esseva executate pro un gruppo de masculos e femininas de etates de infra 30 annos e pro un altere gruppo de individuos normal de etates de supra 50 annos, e le variationes de forma e dimension del fortias ballistocardiographic esseva studiate. Durante le expiration e como effecto de etates plus avantiate, le unda systolic lateral IJ augmenta su dimensiones in comparation con le unda capite-pede IJ. Se impone le conclusion que le classic ballistocardiogramma capite-pede rende inadequate informationes super le fortias liberate in le phase systolic, specialmente in masculos de etates plus avantiate.

References

[1] Bixby, E. W. and Henderson, C. B.: A method of securing the direct body ballistocardiogram by means of a microscope, giving a record readily calibrated. Circulation **8:** 578, 1953.

[2] Brandt, J. L., Caccese, A., Dock, W. and Schrager, A.: The motion of the thorax during the heart cycle: a comparison of longitudinal, lateral and dorsoventral ballistocardiograms. J. Clin. Invest. **30:** 971, 1951.

[3] (a) Braunstein, J. R., Oelker, C. E. and Gowdy, R. C.: Design of a two-dimensional ballistocardiograph. J. Clin. Invest. **29:** 1219, 1950.

(b) Braunstein, J. R.: The Ballistocardiogram. Springfield, Charles C Thomas, 1953.

[4] Brown, H. R., Jr., deLalla, V., Jr., Epstein, M. A. and Hoffman, M. J.: Clinical Ballistocardiography. New York, Macmillan, 1952.

[5] Cerlitti, A. and Weisel, W.: quoted by Dock and associates.[6]

[6] Dock, W., Mandelbaum, H. and Mandelbaum, R.: Ballistocardiography. St. Louis, C. V. Mosby, 1953.

[7] —: The value of lateral ballistocardiograms in differentiating aortic tortuosity from myocardial dysfunction. Am. J. M. Sc. **228:** 125, 1954.

[8] Edson, J. N., Dickes, R., Flamm, G. H. and Tobin, M.: Higher frequency phenomena in the normal ballistocardiogram. Circulation Research **1:** 405, 1953.

[9] Franzblau, S. A., Best, W. R., Marbarger, J. P. and Gullemin, V., Jr.: Three-dimensional vector ballistocardiography (abstract). J. Lab. & Clin. Med. **36:** 824, 1950.

[10] Hamilton, W. F., Dow, P. and Remington, J. W.: The relationship between the cardiac ejection curve and the ballistocardiographic forces. Am. J. Physiol. **144:** 557, 1945.

[11] Samet, P., Mednick, H. and Schwedel, J. B.: Electrokymographic studies of the relationship between electrical and mechanical asynchronism in the cardiac cycle. Am. Heart J. **39:** 841, 1950.

[12] Scarborough, W. R., Beser, J., Talbot, S. A., Mason, R. E., Singewald, M. L. and Baker, B. M., Jr.: A method for recording ballistocardiographic vectors. Bull. Johns Hopkins Hosp. **87:** 235, 1950.

[13] —, Davis, F. W., Baker, B. M., Mason, R. E. Singewald, M. L., Lore, S. A. and Fox, L. M.: A ballistocardiographic study of 369 apparently normal persons. Am. Heart J. **45:** 161, 1953.

[14] —, McKusick, V. A. and Baker, B. M., Jr.: The ballistocardiogram in constrictive pericarditis. Bull. Johns Hopkins Hosp. **90:** 42, 1952.

[15] Smith, J. E.: Comparison of the displacement, velocity, and acceleration ballistocardiogram in coronary heart disease. Am. Heart J. **46:** 692, 1953.

[16] Soldati, L. De., Navarro Viola, R., Mejia, R. H.: El balistocardiograma obtenido con el procedimiento electromagnetico de Dock en sujetos normales. Rev. Argent. cardiol. **18:** 137, 1951.

[17] Starr, I. and Schroeder, H. A.: Ballistocardiogram. II. Normal standards, abnormalities commonly found in diseases of the heart and circulation, and their significance. J. Clin. Invest. **19:** 437, 1940.

[18] — and Hildreth, E. A.: The effect of aging and of the development of heart disease on the ballistocardiogram. Circulation **5:** 481, 1952

[19] — and Schnabel, T. G., Jr.: Further experience with the preparation simulating cardiac function at necropsy. Tr. A. Am. Physicians **66:** 257, 1953.

[20] First Report of the Committee on Ballistocardiographic Terminology. Circulation **7:** 929, 1953.

Pressor Mechanisms Induced by Intracranial Compression

By SIMON RODBARD, M.D. AND WALTER STONE, A.B.

A sudden rise in intracranial pressure initiates a three-fold cardiovascular response in the dog. Within one second after the onset of compression, the blood pressure rises sharply, presumably as a result of a direct neurogenic stimulus to the arterioles; the pressure then levels off in a few seconds. A second pressor effect is apparently due to the secretion into the blood stream of graded amounts of nor-epinephrine-like materials at the onset of compression; this rise is delayed about 12 seconds, a period perhaps associated with its circulation to the arterioles. In some experiments, a heart rate increase occurs at this time. It is shown by a special technique that the circulating blood volume increases about 10 per cent during this period. With the offset of compression all these effects disappear in the same order. The potential role of these mechanisms in the blood pressure regulating complex is discussed.

THE technic of intracranial compression lends itself admirably to the study of some of the mechanisms involved in the regulation of the blood pressure. This is so since the intensity of the pressor response can be shown to be related to the degree of the compression.[1, 2] The stimulus can thus be graded in terms of millimeters of mercury and can be compared with an equidimensional response in blood pressure.

At the turn of the century Cushing[1] demonstrated that the pressor response was dependent on a disturbance in the blood supply to the brain. He interpreted his findings as demonstrating that the stimulus for the rise in pressure was the production of an ischemia or anemia of the brain. His general results have been confirmed by numerous investigators[2-11] who have added significant information concerning the pathways involved. Thus, it has been shown that intracranial compression can produce a blood pressure rise even when most of the brain anterior to the medulla has been removed.[9] The pressor response does not occur if the sympathetic nervous system is eliminated surgically or pharmacologically by section of the spinal cord or by block of its outflow by local anesthetics.[1, 2, 6, 8] Further, an association between the blood pressure adjusting mechanisms of the carotid sinus region with those of intracranial compression is shown by the fact that denervation of the carotid sinus enhances the pressor response to intracranial compression.[2, 5]

Our studies[2] have shown that the data of Cushing as well as of others can be reinterpreted as indicating the presence of a pressor receptor mechanism inside the cranium. This receptor appears to be responsive to differences in the relative pressure existing between that in the blood vessels and that in cerebrospinal fluid. Thus, a rise in the intracranial pressure may be considered the equivalent of a relative fall in the pressure inside cephalic blood vessels. In this way a baroceptor is stimulated, setting a chain of pressor reactions into motion.

In the present study we undertook to determine more accurately the types of pressor mechanisms induced by intracranial compression. Evidence has already been presented to show that in the chick, the pressor response is due primarily to the release of graded amounts of a pressor material into the blood stream depending on the degree of compression. The presence of a relatively long lag, before the onset of the pressor response, suggested the operation of a hormonal factor. The active material was shown to be pharmacologically similar to norepinephrine. However, the very short duration of the lag of the

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

This department is aided in part by the Michael Reese Research Foundation. This study was supported by a grant from the U. S. Army Air Forces.

response in experiments on rabbits and dogs raised the question that pressor mechanisms other than those dependent on circulating pressor materials[12, 13] must be involved in these species. Experiments were therefore undertaken in dogs to analyze the mechanisms available for the production of the rise in blood pressure.

I. "Intact" Preparations

Methods and Results

Twelve dogs weighing 6 to 20 Kg. were anesthetized with intravenous pentobarbital sodium (25 mg. per kilogram). A hole was trephined in the parietal bone near the midline of the skull and the dura was incised. A metal pipe was fitted into the trephine hole and connected to a reservoir of saline. Other details of the preparation have been described previously.[2, 12, 13] Both vagus nerves were then cut and the trachea was cannulated for positive pressure respiration. The femoral artery was cannulated for blood pressure registration and attached to a Sanborn electromanometer. Simultaneous blood pressure and intracranial pressure recordings were made on a direct writing twin-viso cardiette (Sanborn).

Blood pressure response. The intracranial pressure was raised within the course of a second or so to either 200 or 250 mm. Hg, a level considerably above the arterial blood pressure. The onset of the pressor response to this intracranial compression became manifest within two or three heart beats, usually, within one second (fig. 1). Occasionally, this *immediate* response was absent.

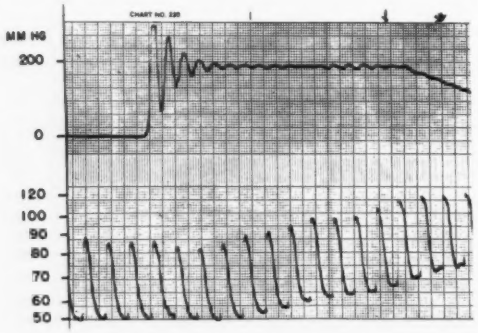


Fig. 1. Acuity of blood pressure response to raised intracranial pressure. Upper line shows acute onset of intracranial compression. Poor damping permitted the intracranial pressure to fluctuate about 200 mm Hg several times before it came to rest slightly below this level. Lower curve shows arterial blood pressure. Each large square equals 0.20 second. Note that the diastolic level begins to rise within one second. Discussed in text.

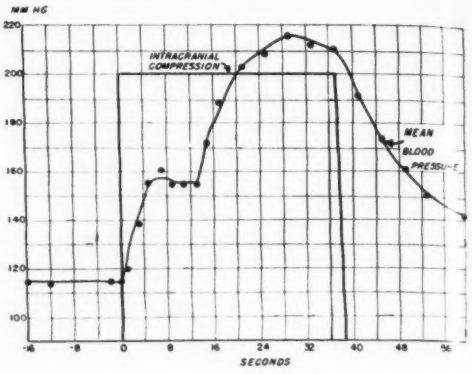


Fig. 2. Two-phase character of blood pressure response to intracranial compression. Time given in seconds as noted. Vertical axis is in millimeters of mercury. Note the pressure rise almost instantly with the onset of intracranial compression at the heavy vertical line. After about 14 seconds, when the pressure has levelled off, a second rise in pressure begins, carrying the blood pressure level above that of the intracranial pressure. With the offset of compression at the second heavy vertical line, the blood pressure begins to fall sharply. Discussed in text.

After another 10 to 25 seconds, when the pressor response appeared to be leveling off, a second, *delayed* blood pressure response with an increased slope usually appeared (fig. 2), and the blood pressure increased to a higher level, usually sufficient to overcome the intracranial compression.

At the offset of intracranial compression there was usually a slow fall in blood pressure to the control level. However, occasionally there were variations in this pattern, with the occurrence of either a rapid fall or of a prolonged pressor response, maintaining the blood pressure at its heightened level for 20 to 30 seconds before the onset of a gradual decline to the control level. The heart rate response to compression was variable.

Comment. The *immediate* blood pressure rise occurring with the onset of intracranial

compression makes it appear unlikely that ischemia or anoxia acts as the triggering device activating the blood pressure regulating mechanism. Instead, it supports the concept that a mechanism depending on pressure sensitivity is involved. The immediate response also indicates that a direct neurogenic vasoconstrictor action on the systemic arterioles is operative.

The increased slope of the blood pressure curve seen 10 to 20 seconds following the onset of the first rise may depend in part on the delayed action of a circulating pressor material. This is in line with evidence from earlier experiments on the chick which had suggested that intracranial compression may trigger the release into the systemic venous blood stream of graded amounts of a pressor agent.

To obtain further information on the nature of these responses, the venous return was measured by modifying the preparation described above.

II. "Open Chest" Preparation

Method and Results

The chest was opened in the third or fourth intercostal space. The superior and inferior venae cavae were cleaned, and the phrenic nerve was dissected away. The azygos vein was ligated at its junction with the superior vena cava. To permit the collection of both superior and inferior vena cava blood the right external jugular vein was isolated and a long polyethylene catheter of 6 or 8 mm. internal diameter was inserted into it (fig. 3). Ligatures were placed above and below the junctions of the right atrium with the vena cava to prevent caval blood flow from passing directly into the right heart. The venous return was collected by means of slight suction (4 to 5 mm. Hg) into a calibrated bottle reservoir. It was then pumped at a constant rate through a meter pump (Maisch) through a flow meter (rotameter) and then returned to the right heart via a cannula tied into the right auricle.

With this preparation it was possible to measure the entire venous return except for the relatively small volume returning to the heart via the coronary sinus, Thebesian veins, and the bronchial arterial supply. Volume calibrations of the reservoir bottle permitted a measure of changes in the venous return from the constant volume being returned to the heart by the metering pump arrangement.

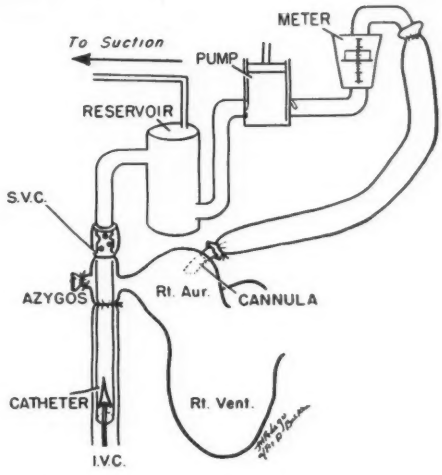


Fig. 3. Apparatus for measuring the venous return and maintaining a constant volume input into the right atrium. Flow passes through venae cavae into catheter and thence to reservoir. It is then pumped via a constant output pump through a flowmeter into the right atrium. Details in text.

A. Blood pressure response. As in the "intact" preparations, the pressor response usually began immediately following the onset of compression (fig. 4). However, significant differences in the character of the blood pressure responses were seen in these open-chest preparations, when compared with those obtained in the "intact" dog. The time of onset of the second, (delayed) rise could be made out occasionally and then without the clear separation of slope seen in the more intact preparations. In the open-chest animal the response was usually less in degree than in the intact dog.

When the intracranial compression was released, the blood pressure began to fall more sharply than in the intact preparations. In the course of 10 seconds or so the pressure often fell to the original level or even markedly below this level. In the latter instances, the pressure then slowly regained its original control value. Sometimes, an overshoot to a new

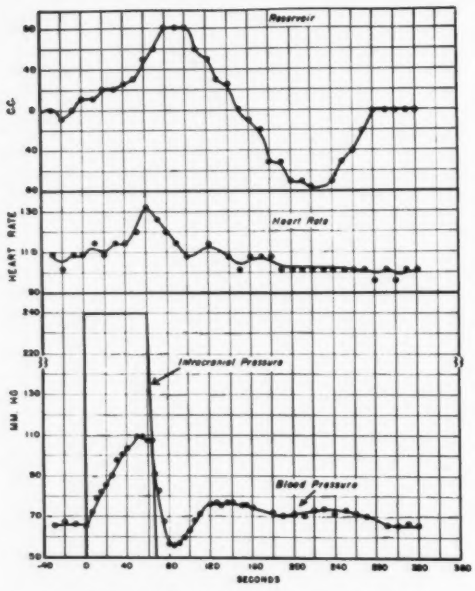


FIG. 4. Data obtained in an experiment on an open-chest preparation. Intracranial pressure and blood pressure are shown in the lowest two curves, as in figure 1. Heart rates are plotted in the central portion of the figure. The top tracing represents the level of the reservoir; this gives a measure of the difference between the constant output and the return of blood via the venae cavae. Discussed in text.

level somewhat higher than that obtaining prior to stimulation was observed.

A greater degree of blood pressure instability was noted in the open-chest preparation. Commonly, a slow fluctuation of the blood pressure level was present, suggesting the operation of a level-seeking device.

B. Heart rate. A gradual rise in heart rate sometimes began about 15 seconds after the onset of compression (fig. 4). The data are tabulated in table 1 which shows the rise in 7 of 12 successive trials. After a lag following the offset of compression, the heart rate returned to control levels.

C. Venous return. Previous studies from this laboratory have suggested that the pressor response to intracranial compression might be dependent in part on a mobilization of a volume of blood from the periphery.[13] This possibility could be tested in the present preparation since a measure of the venous return is provided.

The slight negative pressure applied to the great veins pulls blood from these vessels and their tributaries, presumably to a constant degree. The returned blood is then collected in the reservoir (fig. 3). The constancy of output volume from the pump which takes reservoir blood and passes it into the right atrium makes it possible to measure variations in the venous return. Thus, changes in the level of the blood in the reservoir reflect a difference between the constant rate being ejected by the pump and the potentially variable volume being returned from the veins. An increased venous return is evidenced by a rise in the level of the reservoir while a decreased venous return presents itself as a fall in this level.

At the onset of the intracranial compression no immediate change in venous return was noted (fig. 4). The blood level in the reservoir gradually but consistently began to increase 50 to 100 ml. over the course of 10 to 20 seconds.

The special design of our apparatus withheld this added volume from the circulation. It thus separated the potential effects of this enhanced return from other pressor and cardioaccelerating mechanisms.

No immediate change in the reservoir level was seen at the offset of intracranial compression. After about 15 to 25 seconds, however, a time when the arterial tension had usually fallen sharply from the maximal pressure levels, the reservoir level began to fall. This fall was rapid at first and then took place more gradually as the blood pressure approached control levels (fig. 4). In other experiments a more striking volume effect was seen.

At the end of the compression period the blood pressure fell more sharply than in the "intact" preparations, and sometimes fell markedly below the original control levels. The venous reservoir level also began to fall sharply indicating that less blood was returning to the veins than the constant volume being metered by the pump into the right heart. This would suggest that to halt the sharp fall in pressure, a vasoconstriction was induced which had the

TABLE 1.—*Heart Rate Changes Following Onset and Offset of Intracranial Compression*

Time seconds	Expt. 11 Beats/Min			Expt. 12 Beats/Min.			Expt. 13 Beats/Min.			Expt. 14 Beats/Min.	
Compression											
0	105	105	105	168	174	174	192	190	180	105	108
10	105	113	105	174	168	174	192	190	180	105	114
20	113	105	113	168	168	180	194	194	182	98	108
30	113	105	113	174	194	180	186	194	182	98	114
40	120	105	120	180	180	180	↓	194	182	98	114
50	120	113	128	174	174	186	↓	↓	182	105	114
60	120	120	135	180	↓	↓	↓	↓	↓	112	132
70	128	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Release											
0	126	128	128	174	174	186	186	196	182	128	132
10	126	120	128	174	180	186	186	196	182	112	120
20	113	120	120	180	174	188	186	196	182	112	108
30	113	113	113	174	174	180	186	196	178	105	114
40	113	113	105	168	174	180	180	196	178	105	108
50	105	113	113	160	168	180	180	190	178	112	108
60	105	105	105	168	174	174	189	190	174	105	108

effect of holding blood on the arterial side of the circulation, thereby reducing the venous return to the heart. As the blood pressure finally returned to and was maintained at the normal levels, the amount of blood in the reservoir also gradually returned to its control volume.

DISCUSSION

The present studies provide new information concerning factors initiating the pressor response to intracranial compression as well as an analysis of the mechanisms whereby the rise in blood pressure is accomplished. From the data of our experiments it appears that there are three distinct types of pressor mechanisms involved in the response to intracranial compression. These are summarized in figure 5.

The very brief lag from the onset of compression, less than one second in duration, argues against the possibility that the pressor effect depends upon the development of an ischemia or anemia of the brain. Instead this evidence is in accord with our previous interpretation that the response depends upon a mechanoceptor which reacts immediately to a change in the balance of pressures inside and outside a sensing arterial wall inside the cranium. The immediacy of the response also shows that a direct nervous connection from receptor to effector must be in operation.

There was also a very short delay, of the order of about one second, after the release of intracranial compression before the onset of the fall in blood pressure, expecially in the open-chest preparations. This finding also fits with the evidence that the direct neurogenic vasoconstriction operative during compression ceases almost instantaneously with the return of the intracranial pressure to normal levels.

The second phase of the rise in blood pressure response occurs about 10 to 15 seconds after the onset of intracranial compression. The lag is consistent with our earlier interpretations that a pressor material released into the venous system by the intracranial stimulus is delayed by the amount of time required for circulation to its site of action at the arterioles.[2]

It is of interest to note the similarity between the delayed response and the entire pressor response to intracranial compression which was seen in the chick.[2] It would appear that in the dog the direct vasoconstrictor response is an additional mechanism added to

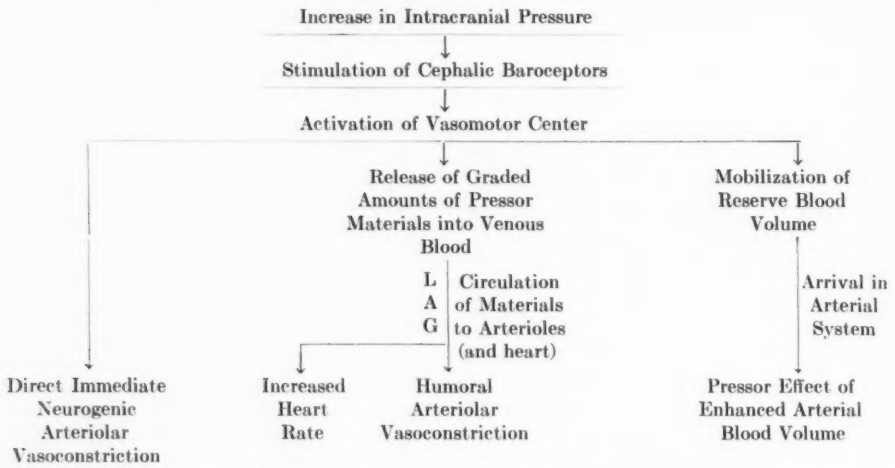


FIG. 5. Mechanisms Involved in the Pressor Response to Intracranial Compression.

that present in the chick, providing a more highly developed and faster vascular response.

The increase in heart rate which sometimes occurs about the same time as the second rise in blood pressure suggests that the substance released into the circulation is one that may have a positive chronotropic effect on the heart. Heymans[14] and Edholm[15] in studies on intracranial pressure have demonstrated such an increased rate after an initial bradycardia. (The vagi were intact in their preparations.) The tachycardia could not have been due to the release of vagus inhibition in our experiments since our animals were all vagotomized bilaterally. It cannot be due primarily to an enhancement of venous return since this heart rate effect occurs in the open chest preparation in which the venous return is maintained constant.

In previous studies we have shown an increased flow of blood through both venae cavae beginning shortly after intracranial compression.[13] The present experiments demonstrate that an amount of blood equivalent to about 10 per cent of the circulating blood volume is mobilized within a few seconds after compression, and added to the effective circulating blood volume.

The pressor responses were consistently greater in the "intact" preparation than in the open chest preparations. This difference must have been due in part to the fact that the enhanced venous return which certainly plays a role in the magnitude of the response was prevented from acting in the open chested preparations by virtue of its entrapment in the pump-reservoir. Other factors presumably include the relatively greater trauma as well as the loss of some vascular-control mechanisms resulting from opening the chest.

This difference between the two types of preparations was also apparent at the release of intracranial compression. In the open-chest preparation there was a very short delay, of the order of about one second, before the onset of the fall in blood pressure. It would not seem probable that in this short period the amount of blood pumped to the central nervous system could carry enough oxygen to overcome the ischemia present, because of the almost negligible diffusion during intracranial compression.

The present study demonstrates the variety of blood pressure regulating mechanisms available to the animal and set into motion by stimulation of the presumptive cephalic baroceptors. These include direct vasoconstrictor and hormonal pressor factors as well as appropriate adjustments of the blood volume.

The possible functions of the intracranial baroceptor-pressor mechanism is also worthy of comment. It would appear unlikely that

such a sensitive pressure regulating system would have developed to meet the rare exigencies of accidental or traumatic increases in intracranial pressure. More likely, the apparatus which we have been studying is a more continually operable system serving a more significant function, probably in the normal regulation of the blood pressure which helps to adjust intracranial blood flow to need.

Similarities between the types of pressor responses induced by the nondiscriminating stimulation of concussion,[16, 17] in which pressor responses are sometimes present, and by localized stimulation of the brain stem[18] suggest the operation of common pathways. Elucidation of these mechanisms may have value in improving our understanding of normal blood pressure regulating mechanisms and perhaps those involved in the genesis of systemic hypertension.

Summary

The response to intracranial compression in dogs subjected to anesthesia and bilateral vagotomy is shown to result from a combination of three types of pressor mechanisms. An immediate rise in pressure, beginning within one second of the onset of intracranial compression, indicates the activation of a direct vasoconstrictor pathway. The presence of a second delayed pressor response occurring 10 to 15 seconds after the onset of stimulation is consistent with earlier studies demonstrating that a hormonal agent may be secreted into the blood, producing a pressor effect after it circulates to the arterioles. A change in heart rate occurring at this time may represent an increase in circulating hormonal chronotropic materials.

An increase in the venous return also participates in the pressor mechanism. This was elicited by deviating the venous return through a constant output pump. An increase in return equivalent to about 10 per cent of the circulating blood volume took place about 10 to 25 seconds after the onset of compression. This indicated a mobilization of blood from the periphery which, being added to the circulating blood volume, would participate in the rise in pressure.

Acknowledgment

We are indebted to Mr. Francis Williams for technical assistance in these experiments.

Summario in Interlingua

Un subite augmento del pression intracranial resulta, in le can, in un triple responsa cardiovascular. Intra un secunda post le declaration del compression, le pression sanguinee ascende acutemente (probabilemente in consequentia de un directe stimulo neurogenic del arteriolas) e tunc se nivella in le curso de alicun secundas additional. Un secunde effecto pressorial es apparentemente causate per le secretion a in le circulation de graduate quantitates de materiales norepinephrinoide. Iste ascendita del pression sanguinee es retardate per circa 12 secundas, un periodo possibilemente associate con le circulation verso le arteriolas. In alicun experimentos isto es etiam le momento del occurrentia de un acceleration del battimento del corde. Per medio de un technica special nos has monstrate que durante le periodo mentionate le volumine del sanguine circulante es augmentate per circa 10 pro cento. Post le cessation del compression omne le effectos enumerate dispare in le mesme ordine. Nos discute le rolo potential de iste mechanismos in le complexo del regulation del pression sanguinee.

REFERENCES

[1] Cushing, H.: Some experimental and clinical observations concerning states of increased intracranial tension. Am. J. M. Sc. **124:** 375, 1902.

[2] Rodbard, S. and Saiki, H.: Mechanism of the pressor response to increased intracranial pressure. Am. J. Physiol. **168:** 234, 1952.

[3] Eyster, J. A. E.: Clinical and experimental observations on Cheyne-Stokes respiration. J. Exper. Med. **8:** 565, 1906.

[4] —, Burrows, M. T. and Essick, C. R.: Studies on intracranial pressure. J. Exper. Med. **11:** 489, 1909.

[5] Guernsey, C. M., Weisman, S. A. and Scott, F. H.: Effect on the reflexes of the carotid sinus of raising the intracranial pressure. Arch. Int. Med. **52:** 306, 1933.

[6] Wright, R. D.: Experimental observations on increased intracranial pressure. Australian & New Zealand J. Surg. **7:** 215, 1937.

[7] Keller, C. J.: Die Regelung der Blutversorgung des Gehirns. Ztschr. f. d. ges. Neurol. **167:** 281, 1939.

[8] Freeman, N. E. and Jeffers, W. A.: Effect of progressive sympathectomy on hypertension produced by increased intracranial pressure. Am. J. Physiol. **128:** 662, 1940.

[9] Forster, F. M.: The role of the brain stem in arterial hypertension subsequent to intracranial pressure. Am. J. Physiol. **139:** 347, 1943.

[10] Kety, S. S., Shenkin, H. A. and Schmidt, C. F.: The effects of increased intracranial pressure on cerebral circulatory functions in man. J. Clin. Invest. **27:** 493, 1948.

[11] Taylor, R. D. and Page, I. H.: Peripheral vasomotor effect of adrenaline and nor-adrenalin acting on the isolated perfused central nervous system. Circulation **4:** 563, 1951.

[12] Reyes, M., Mininni, G. and Saiki, H.: Neurohumoral transmission of the pressor response to intracranial compression. Am. J. Physiol. **176:** 341, 1954.

[13] Rodbard, S. and Stone, W.: Distribution of blood flow through the vena cavae in intracranial compression. Am. J. Physiol. **177:** 504, 1954.

[14] Heymans, C.: The control of the heart rate consequent to changes in the cephalic blood pressure and in the intracranial pressure. Am. J. Physiol. **85:** 498, 1928.

[15] Edholm, D. G.: The relation of heart rate to intracranial pressure. J. Physiol., **98:** 442, 1940.

[16] Scott, W. W.: Physiology of concussion. Arch. Neurol. & Psychiat. **43:** 270, 1940.

[17] Walker, A. E., Kollros, J. J. and Case, T. J.: The physiological basis of cerebral concussion. A. Research Nerv. & Ment. Dis., Proc. **24:** 437, 1945.

[18] McQueen, J. D., Browne, K. M. and Walker, A. E.: Role of the brain stem in blood pressure regulation in the dog. Neurology **4:** 1, 1954.

The Effect of Prolonged Corticotropin Therapy For Rheumatic Fever on the Exchangeable Sodium Content and Body Weight

By JERRY K. AIKAWA, M.D. AND MARIE B. RHYNE, M.D.

WITH THE TECHNICAL ASSISTANCE OF AARON J. BLUMBERG

Serial measurements of the body weight and the exchangeable sodium content were made in young patients with acute rheumatic fever who were being treated with large doses of corticotropin. All but one subject developed the clinical signs of hyperadrenalism. Eight of the 11 subjects showed at least a 20 per cent increase in body weight which could not be explained on the basis of the changes in exchangeable sodium content. This change in body composition is thought to be due primarily to an increase in total body fat.

THE prolonged administration of corticotropin (ACTH) in therapeutic doses is known to produce the physical signs of hyperadrenalism.[1] The increase in body weight resulting from such administration has usually been attributed in large measure to retention and redistribution of sodium and water.[2] This explanation appears to be reasonable in adults, since a decrease in body weight and rapid excretion of sodium often follows the administration of a diuretic agent or the discontinuance of corticotropin.[3] The "moon facies"[1] and the "buffalo hump" observed clinically, however, suggest a more profound change in body composition. To date few studies on the effects of ACTH on fat metabolism have been reported.[4, 5]

In the course of a study on the immunophysiology of rheumatic fever, it became apparent that rheumatic children and adolescents who gained weight while being treated with ACTH did not respond with diuresis when mercurial diuretics were given. The purpose of the present report is to demonstrate the marked discrepancy between the variations in the exchangeable sodium content of the body and the changes in the body weight during prolonged treatment of rheumatic fever with long-acting corticotropin (Acthar gel).

From the Department of Medicine and Pediatrics, University of Colorado School of Medicine, Denver, Colo.

This work was supported in part by a grant-in-aid from the American Heart Association and in part under a contract with the U. S. Atomic Energy Commission.

Dr. Aikawa is an Established Investigator of the American Heart Association.

MATERIAL AND METHODS

Subjects. Eleven subjects, five females and six males, with the diagnosis of acute rheumatic fever were studied. Their ages ranged from 8 to 18 years, and seven patients were under 12 years of age. All subjects showed unequivocal clinical symptoms and signs of acute rheumatic activity as judged by the diagnostic criteria of Jones.[6]

The general plan of therapy was to administer daily a single intramuscular injection of Acthar gel in a dosage of 1 to 2.5 units per lb. (2.0 to 5.7 units per Kg.) of initial body weight and to maintain this dosage until the clinical and laboratory evidences of rheumatic activity had subsided. The dosage of corticotropin was then gradually reduced, unless signs of rheumatic activity recurred, in which case an intermediate dosage was continued for a longer period until all signs of rheumatic activity had again subsided. The longest duration of continuous ACTH gel therapy was more than 90 days, and the shortest, 34 days.

All subjects were placed on a regular hospital diet and received supplemental feedings between meals as desired. All but one individual received oral supplements of potassium chloride, 1 to 2 Gm. thrice daily. Nine also received 200 to 1000 mg. of ascorbic acid daily by mouth.

Isotopes. Isotopic sodium (Na^{24})* was prepared

* Na^{24} was supplied by the Oak Ridge National Laboratory, Oak Ridge, Tenn., on allocation from the U. S. Atomic Energy Commission.

for injection in the manner previously described.[7] The subjects were given 1.5 μc. of Na^{24} per Kg. of body weight, contained in sterile physiologic saline solution.

Determination of Exchangeable Sodium Content (Na-e). Each subject received an intravenous injection of radioactive sodium from a calibrated syringe between 8:30 and 10 a.m. All urine voided for the next 24 hours was collected, and the Na^{24} content of the pooled specimen was determined. A blood specimen was obtained 24 hours after the injection of Na^{24}, and the specific activity of the sodium in the serum was determined. The following formula was used to calculate the value for the exchangeable sodium content of the body:

$$Na\text{-}e = \frac{Na\text{-}i^{24} - Na\text{-}u^{24}}{Na\text{-}s^{24}/Na\text{-}s^{23}}$$

$Na\text{-}e$ = quantity of exchangeable sodium in milliequivalents (mEq.).
$Na\text{-}i^{24}$ = quantity of radiosodium administered (arbitrary units).
$Na\text{-}u^{24}$ = quantity of radiosodium excreted in the pooled specimen of urine.
$Na\text{-}s^{24}$ = concentration of radiosodium in the serum at 24 hours.
$Na\text{-}s^{23}$ = concentration of nonradioactive sodium in the serum at 24 hours.
$Na\text{-}s^{24}/Na\text{-}s^{23}$ = specific activity of the serum at 24 hours.

Preliminary studies in this laboratory revealed that the Na-e measurement was reproducible within five per cent in hospitalized subjects who were convalescing from various diseases.[8] This finding agrees with those previously reported by Miller and Wilson.[9]

A total of 53 determinations of exchangeable sodium content were made; a minimum of three and a maximum of seven serial determinations were performed on each subject, usually at intervals of two to three weeks. Each patient was observed for a minimum of 50 days.

Measurement of Radioactivity. The radioactivity of the urine and serum specimens was determined with a well-type scintillation counter and a scaling circuit. A total of 10,000 counts were made on each sample. All determinations were corrected for decay of the isotope. The total sodium concentration in the serum was determined with a Baird flame photometer, using the lithium internal standard method.

Results (table 1)

Signs of hyperadrenalism. All subjects except one (case 9) showed obvious clinical signs of hyperadrenalism, moon face, cervical and supraclavicular fat pads (buffalo hump) and acne, while being treated with corticotropin. In case 9 some fullness of the face developed by the fourth week of corticotropin therapy, but there were no other obvious manifestations.

No relationship between the development of hyperadrenalism and the effect of corticotropin on the underlying rheumatic process was observed.

Changes in Body Weight (fig. 1). In nine of the 11 subjects the body weight increased by at least 10 per cent (cases 1 to 9). In five of these individuals (cases 1, 2, 3, 5 and 6) the weight gain was more than 25 per cent of the initial value. The greatest rate of increase was observed in the individual (case 1) who received the largest daily dosage of corticotropin (5.7 units per Kg.); on the seventy-fifth and eighty-ninth day, this patient's weight was 65 per cent above the original measurement. Two subjects (cases 10 and 11), although they showed the clinical signs of Cushing's syndrome, failed to gain weight.

Although there was considerable variability, the increase in body weight appeared to be progressive and related to the dosage and the duration of therapy. There was no definite relationship between the changes in body weight and the effect of corticotropin on the rheumatic process.

Changes in Exchangeable Sodium Content (Na-e) (fig. 2). Five subjects (cases 1, 5, 6, 7, and 11) revealed at least a 10 per cent increase in the exchangeable sodium content at some time during the period of observation. In two of these individuals, this increase was observed after treatment with corticotropin was discontinued. In the other three individuals, subsequent values for exchangeable sodium content obtained while the subjects were being treated with corticotropin were equal to the baseline values, or even lower.

In the other six individuals no significant increase in the exchangeable sodium content was demonstrated during corticotropin therapy. In three instances (cases 2, 3 and 4) exchangeable sodium contents 29, 22 and 21 per cent below the initial determinations were obtained while the patients were on corticotropin therapy and while body weight was increasing.

TABLE 1—*The Exchangeable Sodium Content and Body Weight During ACTH Therapy of Rheumatic Fever*

	Age (yr.)	Sex	ACTH Maximum (units/day)	Dose Total (units)	Duration Therapy (days)	Initial Body Wt. (Kg.)	Initial Na-e (mEq.)	Day of Rx	Change in Wt. (Kg.)	Change in Na-e (mEq.)	Unexplained Change in Wt.* (Kg.)	Unexplained Change in Wt.* (% initial Wt.)	Serum Sodium Concentration: Initial value (mEq./L.)	Serum Sodium Concentration: Change (mEq./L.)
	8	M	120	6740	90	20.9	1071	6	+2.7	+265	+0.8	4	137.3	−1.3
								20	+6.8	+533	+2.9	14		+0.6
								34	+6.4	+333	+4.0	19		+9.7
								47	+7.2	+283	+5.1	24		+9.1
								75	+13.6	+157	+12.5	60		+3.7
								89	+13.6	+52	+12.8	61		+1.7
2	11	F	100	5870	80	18.2	1071	11	+0.4	−79	+0.9	5	138.2	+1.4
								23	+0.4	−14	+0.4	2		+9.3
								52	+5.0	−72	+5.5	30		+7.3
								66	+5.0	−207	+6.5	36		+5.8
								80	+5.9	−229	+7.5	41		+0.5
3	9	F	120	6340	80	28.2	1509	20	−0.1	−139	+1.0	4	143.7	−1.7
								62	+6.3	+14	+6.2	22		+1.3
								77	+7.3	−325	+9.5	34		−7.5
4	11	M	65	2828	51	32.0	2043	33	+2.3	−425	+5.2	16	147.8	+3.7
								47	+6.2	−579	+9.0	28		−2.8
								62	+5.0	−597	+9.0	28		−7.3
5	10	F	60	2880	53	26.8	1271	7	+1.7	−66	+1.2	4	138.2	+2.2
								14	+2.1	+31	+1.9	7		+6.9
								42	+6.2	+9	+6.2	23		+7.3
								60	+8.0	+205	+6.5	24		+8.3
6	11	F	60	3540	64	29.9	1474	12	+0.8	−29	+0.8	3	134.6	+2.2
								19	+5.6	−90	+6.0	20		+9.8
								26	+5.7	−27	+5.8	19		+2.2
								41	+5.0	−10	+5.0	17		+9.9
								54	+7.7	+108	+7.0	23		+11.1
								73	+8.2	+196	+6.7	22		+12.9
7	15	M	150	5150	41	46.4	2255	24	+7.7	+780	+2.4	5	146.6	+0.9
								38	+10.3	+547	+6.6	14		+2.4
								53	+7.7	−316	+9.8	21		−10.6
8	14	M	80	4400	64	35.1	1895	10	+0.8	−81	+1.3	4	137.1	+1.1
								17	+1.1	−126	+2.0	6		+3.3
								39	+4.2	−34	+4.5	13		+9.9
								52	+6.0	−131	+7.0	20		+6.1
9	13	F	120	4280	44	58.6	2391	15	+3.4	+50	+3.1	5	136.8	+3.3
								28	+3.1	+132	+2.2	4		+5.7
								58	+5.8	+163	+4.8	8		+8.7
10	11	M	100	5020	66	47.1	1814	48	−3.5	−54	−3.8	−8	136.2	+7.8
								61	−0.9	−14	−1.0	−2		+8.5
11	18	M	150	4450	34	55.4	2467	16	+2.8	+400	0	0	139.4	+5.6
								30	−0.4	−236	+1.3	2		+0.6
								45	+0.1	−217	+1.7	3		−2.9

* Unexplained change in weight (Kg.) = change in weight (Kg.) referable to initial value − change in Na-e (mEq.)/serum sodium concentration (mEq./L.) at the time of each determination.

No relationship was observed between the variations in exchangeable sodium content and the effect of corticotropin on the rheumatic process.

Unexplained Weight Change (fig. 3). This was determined by dividing the change in Na-e by the serum sodium concentration (mEq. per L.) at the time of each determination and

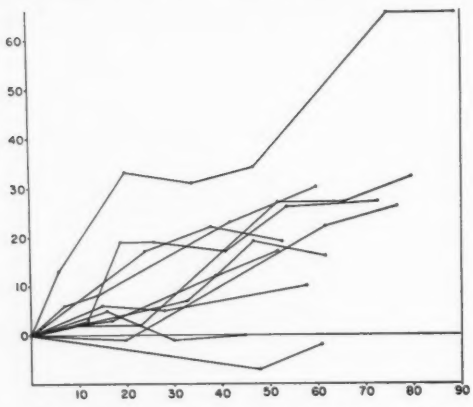


FIG. 1. Weight changes in rheumatic subjects treated with corticotropin. Abscissa shows number of days of therapy; ordinate, changes in body weight (per cent of initial value).

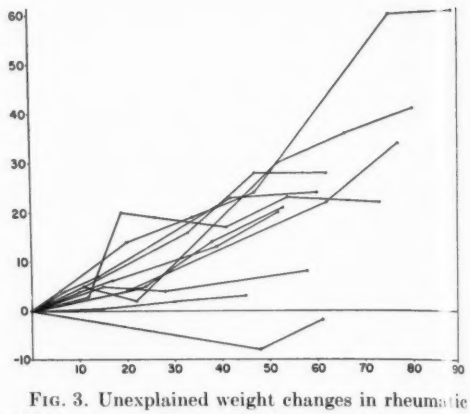


FIG. 3. Unexplained weight changes in rheumatic subjects treated with corticotropin. Abscissa shows days of therapy; ordinate, change in body weight (per cent of initial body weight).

subtracting this result from the change in weight (Kg.) referable to the initial value. When the changes in body weight are correlated with the fluctuations in exchangeable sodium content, it becomes apparent that in 8 of the 11 subjects (cases 1 to 8), an increase of at least 20 per cent in body weight cannot be accounted for on the basis of alterations in the exchangeable sodium content; the assumption is made in this calculation that the changes in exchangeable sodium content are due solely to those in the extracellular fluid sodium. Of the remaining three subjects, one (case 9) did not develop the typical appearance of hyperadrenalism; one developed the clinical signs while he was losing weight (case 10), and the other showed no significant weight change as the moon facies and buffalo hump appeared.

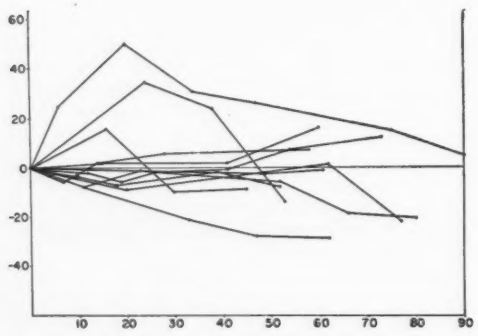


FIG. 2. Changes in exchangeable sodium content during therapy of rheumatic fever with corticotropin. Abscissa shows days of therapy; ordinate, change in Na-e (per cent of initial value).

Changes in Serum Sodium Concentration (table 1). In eight instances the initial serum sodium concentrations, although still within the normal range, was below 140 mEq. per liter. In all of these subjects the serum sodium concentration rose above 145 mEq. per liter while they were being treated with corticotropin. In the remaining three subjects, the initial serum values were between 144 and 148 mEq. per liter. In these individuals, no significant increases were noted during corticotropin therapy.

In some instances (cases 1, 2, 3, 4, 7 and 11) the serum sodium concentration decreased as the dosage of corticotropin was decreased or discontinued.

COMMENT

There are several possible explanations for the fact that the prolonged administration of corticotropin produced increases in body weight which were out of proportion to the changes in exchangeable sodium content: (1) The administration of corticotropin might substantially alter the amount of sodium available for exchange with the radioisotope. (2) The observed changes in weight and Na-e may be due

to a contaminant of the Acthar gel used, such as Pitressin. (3) The initial catabolic effect of corticotropin on protein metabolism may be reversed by prolonged administration, so that body tissue is deposited and body weight increased thereby. (4) There may be an increase in the intracellular water and electrolyte content and osmolarity, or both, without an associated increase in the intracellular sodium content. (5) Prolonged therapy with corticotropin may result in an excessive accumulation of body fat. This may be a specific effect on fat metabolism, or it may be a reflection of an increase in appetite and food intake.[1]

(1) No data are currently available which suggest that corticotropin may alter the exchangeability of sodium.

(2) Although it has been previously suggested[10] that the gain in weight not explained by changes in nitrogen, sodium or potassium may be a Pitressin effect, the lack of diuresis and weight loss on discontinuation of therapy argues against this possibility. Were this simply a retention of water due to an antidiuretic effect, the serum sodium concentration should have fallen.

(3) Although the administration of corticotropin usually results in negative nitrogen and potassium balance, positive nitrogen balance may occur, provided the dietary intake is great enough,[11] and children and adolescents on Acthar gel do have enormous appetites. Therefore, the discrepancy between the increase in body weight and the changes in exchangeable sodium contents can be attributed to an increase in nonextracellular body tissue. While it is recognized that these changes may in part be the effects of normal body growth, it is difficult to explain all of them solely on this basis. In two subjects (cases 10 and 11) signs of hyperadrenalism appeared at a time when both the body weight and the exchangeable sodium content were decreasing. This observation suggests that the signs of hyperadrenalism may be due to a change in body composition relative to an increase in body fat or intracellular water content, rather than to simply an increase in body muscle mass.

(4) In the calculation of the "unexplained weight change", the assumption was made that the change in exchangeable sodium content was a reflection of changes in the extracellular sodium content, although it is recognized that the exchangeable sodium includes nonextracellular reservoirs such as muscle cells and bone. Changes in intracellular water and electrolytes, as well as extracellular water, might explain the observed alterations in body weight and exchangeable sodium content. For instance, if there is no change in intracellular osmolarity, then an unchanged total exchangeable sodium, which includes intracellular sodium, with an increase in body weight would mean that the increase in intracellular fluid would have been due primarily to an increase in potassium. This certainly would not be in the expected direction in patients receiving corticotropin.

The increase in serum concentration of sodium during corticotropin therapy suggests that a redistribution of water into the intracellular phase may have occurred. Such a change could occur as a result of a large change in osmolarity of intracellular solutes or cations. However, the only way in which this intracellular water increase could occur would be by a positive balance of potassium; this would be unlikely during corticotropin therapy. Deane and his co-workers[12] have reported that, in one of two patients with acute rheumatic fever treated with corticotropin, 100 mg. daily for 34 days, the body weight increased progressively from 53.9 to 60.0 Kg. The exchangeable sodium content remained constant, but the total water content increased progressively. These data suggest that the intracellular water content was increased. However, it is difficult to explain increases of 25 to 61 per cent of the body weight, observed in the present series, on this basis alone.

(5) Carcasses of rats treated with corticotropin, when compared with those of controls on the same food intake, have a relative and absolute increase in fat content.[13] The signs of hyperadrenalism produced by the prolonged administration of a relatively large dose of corticotropin resembles those of spontaneous Cushing's syndrome. In the latter condition, deposits of fat, most conspicuously in the face, the neck and the trunk, have been demonstrated by histologic means.[14] Although no

direct evidences regarding this matter are available from this study, it appears most likely that the observed discrepancy between the changes in body weight and the exchangeable sodium content can be attributed in large measure to an accumulation of body fat.

Summary

Serial measurements of the body weight and of the exchangeable sodium content (Na-e) were made in 11 subjects with acute rheumatic fever who were being treated with long-acting corticotropin in daily doses ranging from 2.0 to 5.7 units per Kg.

In all but one subject the typical clinical signs of hyperadrenalism developed. Eight of the 11 subjects showed at least a 20 per cent increase in body weight which was out of proportion to the changes in exchangeable sodium content.

The results suggest that the prolonged therapy of rheumatic fever with adrenocorticotropin results in an alteration in body composition, which is characterized by a relative decrease in body sodium content. It is suggested that the total body fat content may have been increased.

Acknowledgment

We wish to express our appreciation to Dr. Robert H. Alway and the other members of the Department of Pediatrics for their cooperation and assistance.

Summario in Interlingua

Esseva executate mesurationes serial del peso corporee e del contento de natrium excambiabile in juvene patientes con acute febre rheumatic qui se trovava sub tractamento con large doses de corticotropina. Omne le subjectos, con un exception, disveloppava le signos clinic de hyperadrenalismo. In 8 ex le 11 subjectos il occurreva un augmento de al minus 20 pro cento del peso corporee, lo que non esseva explicabile super le base de alterationes in le contento de natrium excambiabile. In nostre opinion iste cambiamento del composition corporee es primarimente debite a un augmento del grassia total del corpore.

References

[1] Sprague, R., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. T.: Observations on the physiologic effects of cortisone and ACTH in man. Arch. Int. Med. **85:** 199, 1950.

[2] Levitt, M. F. and Bader, M. E.: Effect of cortisone and ACTH on fluid and electrolyte distribution in man. Am. J. Med. **11:** 715, 1951.

[3] Eliel, L. P., Hellman, L., Pearson, O. H. and Katz, B.: The Effects of ACTH on the Electrolyte Content of Various Body Tissues. *In*, Proc. of the 2d Clinical ACTH Conference, Mote, J. R., ed. New York, Blakiston & Co., 1951, vol. 1, p. 196.

[4] Kinsell, L. W., Margen, S., Michaels, G. E. and Partridge, J.: Hormonal Regulation of Fat Metabolism. 1. Effects of ACTH and of Certain Steroid Hormones upon Fasting-Induced Hyperketonemia. *In*, Proc. of the 2d Clinical ACTH Conference, Mote, J. R., ed. New York, Blakiston & Co., 1951, vol. 1, p. 308.

[5] Adlersberg, D., Schaefer, L. E. and Drachman, S. R.: Development of hypercholesterolemia during cortisone and ACTH therapy. J.A.M.A. **144:** 909, 1950.

[6] Jones, T. D.: The diagnosis of rheumatic fever. J.A.M.A. **126:** 481, 1944.

[7] Aikawa, J. K.: Comparison of the thiocyanate and radiosodium spaces in disease states. Am. J. M. Sc. **224:** 632, 1952.

[8] Unpublished data.

[9] Miller, H. and Wilson, G. M.: The measurement of exchangeable sodium in man using the isotope ^{24}Na. Clin. Sc. **12:** 97, 1953.

[10] Bartter, F. C., Fourman, P., Albright, F., Forbes, A. P., Jefferies, W. M., Griswold, G., Dempsey, E., Bryant, D. and Carroll, E.: The effect of adrenocorticotropic hormone in panhypopituitarism. J. Clin. Invest. **29:** 950, 1950.

[11] Sprague, R. G.: Cortisone and ACTH. Am. J. Med. **10:** 567, 1951.

[12] Deane, N., Ziff, M. and Bunim, J. J.: Effects of corticotropin on body water and electrolytes in patients with rheumatic disease. J. Clin. Invest. **32:** 879, 1953.

[13] Li, C. H., Simpson, M. E. and Evans, H. M. Influence of growth and adrenocorticotropic hormones on the body composition of hypophysectomized rats. Endocrinology **44:** 71, 1949.

[14] Forbus, W. D. Reaction to Injury. Baltimore, Williams & Wilkins, 1952, vol. 2.

Alterations in Exchangeable Sodium Content, "Sodium^{24} Space" and Body Weight During The Treatment of Congestive Failure

By JERRY K. AIKAWA, M.D. AND REGINALD H. FITZ, M.D.

WITH THE TECHNICAL ASSISTANCE OF SEYMOUR H. LEVITT, M.D., AARON J. BLUMBERG AND MARIE B. RHYNE, M.D.

Serial determinations of the exchangeable sodium content and sodium^{24} (Na^{24}) space were made by the radioisotope dilution method in patients with congestive failure during the course of intensive therapy. In most instances, the decrease in body weight was too great to be accounted for solely on the basis of the change in sodium^{24} space or exchangeable sodium content. This excess weight loss is attributed to loss of intracellular fluid.

INCREASE in body weight, which occurs during congestive heart failure, was generally assumed to be due to the retention of sodium and water in the extracellular fluid compartment. However, some recent studies have suggested that changes also occur in the intracellular phase.[1, 2] The external balance method, which has been used in most previous studies of this problem does not permit the direct measurement in vivo of the sodium content of the body. This difficulty can be overcome by the use of the isotope dilution technic, and one group of investigators[3] has previously reported such an application of this technic.

The purpose of the present study was to determine, by the use of the in vivo isotope dilution technic, whether or not the weight loss which occurs during diuresis can be accounted for solely on the basis of a decrease in the extracellular content of sodium and water. Serial determinations of the exchangeable sodium content were made and the changes in this value were correlated with the alterations in body weight. Observations were also made on the effects of intensive therapy with mercurial diuretics on sodium and potassium metabolism.

From the Department of Medicine, University of Colorado School of Medicine, Denver, Colo.

This work was supported in part by grant-in-aid from the American Heart Association and Wyeth Laboratories, and in part under a contract with the U. S. Atomic Energy Commission.

Dr. Aikawa is an Established Investigator of the American Heart Association.

MATERIAL AND METHODS

Subjects. Thirteen patients, 9 men and 4 women, with advanced congestive failure were studied. Their ages ranged from 53 to 77 years. In five subjects, the cause of the congestion was pulmonary fibrosis and emphysema with cor pulmonale; in six subjects, coronary arteriosclerotic heart disease; and in two, hypertensive cardiovascular disease. Most of these individuals had previously been followed in the Outpatient Clinic and had received maintenance doses of digitalis, ammonium chloride and aminophylline, and periodic injections of a mercurial diuretic. Only one patient (case 2) had not previously been treated with digitalis or a mercurial diuretic. When admitted to the hospital, all were edematous.

The general plan was to make serial determinations of the exchangeable sodium content, the radiosodium space, the serum concentrations of sodium and potassium, and the body weight during hospitalization.

All patients received a salt-free or low-salt (200 to 400 mg.) diet; water was given without restriction. Except in one case, mercaptomerin sodium (Thiomerin) was administered subcutaneously or intramuscularly whenever mercurial diuretics were indicated. A summary of the clinical data and the type of therapy employed is given in table 1.

Isotopes. Isotopic sodium (Na^{24})* was prepared for injection in the manner previously described.[4]

Measurement of Radioactivity. The activity of the urine and serum specimens was determined with a well-type scintillation counter and a scaling circuit.

* Na^{24} was supplied by the Oak Ridge National Laboratory, Oak Ridge, Tenn., on allocation from the U. S. Atomic Energy Commission.

A total of 10,000 counts were made on each sample. All determinations were corrected for decay.

Determination of Serum Sodium and Potassium. The total sodium and potassium concentrations in the serum were determined with a Baird flame photometer, using the lithium internal standard method.

Procedure

Determination of Exchangeable Sodium Content (Na-e). Each subject received from a calibrated syringe 1.5 μc. of Na^{24} per Kg. of body weight, contained in sterile 0.9 per cent sodium chloride solution. All urine voided for the next 24 hours was collected, and the Na^{24} content of the pooled specimen was determined. A blood specimen was obtained 24 hours after the injection of Na^{24} and the specific activity of the sodium in the serum was determined.

Calculations. The following formula was used to calculate the value for the *exchangeable sodium content* of the body:

$$Na\text{-}e = \frac{Na\text{-}i^{24} - Na\text{-}u^{24}}{Na\text{-}s^{24}/Na\text{-}s^{23}}$$

$Na\text{-}e$ = quantity of exchangeable sodium in milliequivalents (mEq.).
$Na\text{-}i^{24}$ = quantity of radiosodium administered.
$Na\text{-}u^{24}$ = quantity of radiosodium excreted in the pooled specimen of urine.
$Na\text{-}s^{24}$ = concentration of radiosodium in the serum at 24 hours.
$Na\text{-}s^{23}$ = concentration of nonradioactive sodium in the serum at 24 hours.
$Na\text{-}s^{24}/Na\text{-}s^{23}$ = specific activity of the serum at 24 hours.

Preliminary studies in this laboratory revealed that the Na-e measurement was reproducible within five per cent in edema-free, hospitalized subjects with various chronic diseases whose condition was stabilized. This finding agrees with those previously reported by Miller and Wilson.[5]

Sodium^{24} Space. The volume of dilution of the injected Na^{24} was calculated as follows:

$$Na^{24}\ space\ in\ liters = \frac{total\ sodium^{24}\ activity\ injected}{serum\ Na^{24}\ concentration\ per\ liter\ at\ 24\ hours}.$$

A total of 35 determinations of exchangeable sodium content and radiosodium space were made on 13 subjects, usually at weekly, but occasionally at biweekly intervals.

Results (table 1 and 2)

Weight Changes. All 13 subjects lost weight during the period of observation. The maximum decrease in body weight (25 per cent of the original value) occurred in the subject (case 2) with the shortest duration of acute congestive heart failure (one week). This subject, on intensive mercurial therapy, rapidly lost 14.1 Kg., in spite of which the serum sodium concentration remained normal and unchanged. Transient small increases in weight (1 and 3 per cent) occurred in two subjects (cases 3 and 4), and were followed by subsequent decreases in weight. One of these subjects (case 4) died in congestive heart failure four days after completion of the third determination of exchangeable sodium content (Na-e).

Exchangeable Sodium Content. The mean exchangeable sodium content in older adult male subjects with congestive heart failure has been previously reported to be 56.7 ± 1.9 mEq. per kilogram.[3] In the present series, the mean of the initial values was 65.3 ± 3.2 mEq. per kilogram. In only one instance (case 13) was the original value for Na-e/Kg. within the normal range (40.6 ± 1.5 mEq. per kilogram).[3] This subject was a markedly obese woman who had clinical evidences of congestive heart failure and in whom the Na-e value subsequently decreased during therapy.

In 11 of the 13 patients, the final values for exchangeable sodium content per kilogram were above the range previously reported (3) in individuals who had cardiovascular disease without congestive heart failure (42.8 ± 2.4 mEq. per kilogram.)

In all instances except one (case 4), the absolute values for Na-e decreased during the period of observation. This decrease was greater than 30 per cent of the original value in five subjects (cases 2, 3, 8, 9 and 11); in absolute values the decrease ranged from 1310 to 2132 mEq. The patient who failed to show any decrease was a man who did not respond to intensive treatment and who died four days after the last determination (case 4).

In figure 1 the change in weight has been plotted against the change in exchangeable sodium content and serum sodium concentration. If 1 Kg. of weight loss is assumed to represent 1 L. of extracellular fluid water, then each kilogram of weight loss should be accompanied by a loss of sodium equivalent to its concentration in the serum at that instant. This nor-

TABLE 1—*Determinations of Exchangeable Sodium Content, Radiosodium Space, and Body Weight During Intensive Therapy of Congestive Heart Failure*

Case	Age (Yrs.)	Sex	Cause of Congestion	Pertinent Clinical Data	Therapy*	Days of Hospitalization	Weight (kg.)	Exchangeable Sodium Content		Radiosodium Space		Serum Concentrations	
								Total (mEq.)	Na-e/wt. (mEq./Kg.)	Total (L.)	(ml./Kg.)	Sodium (mEq./L.)	Potassium (mEq./L.)
1	53	M	ASHD	Chr. congest.; readmitted 2 wks. after previous discharge. Disoriented between 5th and 12th hospital days.	1, 4, 7 (2 ml. q day x 7)	5	53.6	4282	80.5	31.3	58.8	136.8	4.6
						12	46.8	3478	74.3	24.3	52.0	142.9	2.7
2	72	M	ASHD	One prev. episode 2 yrs. ago. Duration present bout, 1 wk.	2, 7 (1 ml. q day x 8)	1	56.6	4407	78.0	31.3	55.3	141.0	3.8
						9	42.5	2275	53.5	16.0	37.7	142.0	4.3
3	77	M	ASHD	Chr. congest., initially refractory to therapy.	1, 3, 4, 7 (2 ml. q.o.d. x 19)	13	68.2	5246	76.9	38.7	56.7	135.7	3.3
						20	70.2	5147	73.3	37.2	53.1	138.2	5.1
						34	63.6	5462	85.9	40.9	64.3	133.5	4.1
						45	59.5	3276	55.0	24.7	41.5	132.7	4.6
4	56	M	Cor P.	Chr. edema; died on 19th hospital day.	1, 3, 7 (2 ml. x 3 in 4 days)	2	73.0	5560	76.2	44.7	61.3	124.3	4.3
						8	73.5	5923	80.6	45.6	62.0	130.0	4.0
						15	70.9	5641	79.6	38.8	54.7	145.5	3.8
5	55	F	Cor P.	Congest. for 4 yrs. Severe dyspnea 2 wks. Obese	1, 6, 3, 7 (2 ml. x 2)	2	67.8	4897	72.2	35.1	52.9	139.3	5.1
						9	60.5	4130	68.3	30.5	50.4	135.4	3.6
6	62	M	Cor P.	Congest. for 3 mos.	1, 3, 4, 7 (1 ml. q day x 9)	8	56.4	3591	63.7	27.0	47.8	133.2	3.8
						16	51.4	3220	62.7	23.0	44.7	140.4	4.3
7	64	M	Cor P.	Parox. dyspnea for 10 yrs.	1, 3, 4, 7 (2 ml. x 1)	1	45.5	2887	63.5	21.2	46.7	136.0	5.0
						8	42.3	2230	52.7	18.1	42.9	123.0	5.3
8	68	M	ASHD	Periph. edema, 1 yr. Dyspnea, 2 wks.	1, 3, 4, 8, 7 (2 ml. x 1)	2	77.3	4893	63.3	37.0	47.8	132.4	4.4
						9	68.6	3344	48.7	22.5	32.8	148.4	4.7
						16	60.0	3674	61.2	26.8	44.7	137.1	4.0
9	60	M	HCVD	Congest. 4 yrs. Massive periph. edema, 6 wks.	1, 3, 4, 7 (1 ml. q.o.d. x 11)	7	68.2	4314	63.3	30.2	44.2	143.0	4.6
						14	60.5	3497	57.8	25.8	42.7	135.4	4.4
						21	55.0	2680	48.7	20.8	37.7	129.1	4.5
						28	52.7	2383	45.2	17.9	34.0	132.9	4.4
10	75	F	ASHD	Increasing dyspnea and leg edema for 2 mos.	1, 4, 6, 7 (2 ml. x 3)	2	65.2	4117	63.1	31.1	47.7	132.5	
						16	58.1	3876	66.7	28.2	48.6	137.4	3.8
						24	60.3	3713	61.6	27.1	45.0	137.0	4.1
						31	58.8	3857	65.6	27.9	47.4	138.3	4.2
11	63	F	HCVD	Massive edema for 3 wks.	1, 4, 7 (2 ml. x 3)	4	73.5	4245	57.8	32.4	44.0	131.2	3.7
						12	61.8	2935	47.5	23.1	37.4	127.0	4.6
						19	61.8	3200	51.8	23.0	37.3	139.0	5.1
12	74	M	Cor P.	Congest. continually for 1 yr.	1, 7 (1 ml. q.o.d. x 7)	7	60.9	3100	50.9	23.3	38.2	133.2	4.5
						22	57.3	2946	51.4	20.8	36.3	141.7	4.9
13	77	F	ASHD	Congest. 4 mos. Marked obesity.	1, 7 (1 ml.)	3	83.6	3328	39.8	25.2	30.1	132.3	4.1
						11	77.7	2651	34.1	19.4	24.9	136.8	4.9

* 1 = Digitalis in maintenance doses.
2 = Rapid digitalization while hospitalized.
3 = Aminophylline suppositories.
4 = Ammonium chloride.
5 = Potassium chloride.
6 = Diamox.
7 = Dosage of mercurial diuretic (Thiomerin).

TABLE 2—*Changes in Exchangeable Sodium Content, Radiosodium Space and Body Weight During Intensive Therapy of Congestive Heart Failure*

Case	Day of Hospitalization	Change in Weight*		Change in Exchangeable Na*		Change in Radiosodium Space*	
		(%)	(Kg.)	(%)	(mEq.)	(%)	(L.)
1	12	−13	−6.8	−19	−804	−22	−7.0
2	9	−25	−14.1	−48	−2132	−49	−15.3
3	20	+3	+2.0	−2	−99	−4	−1.5
	34	−7	−4.6	+4	+216	+6	+2.2
	45	−13	−8.7	−38	−1970	−36	−14.0
4	8	+1	+0.5	+7	+363	+2	+0.9
	15	−3	−2.1	+1	+81	−13	−5.9
5	9	−11	−7.3	−16	−767	−13	−4.6
6	16	−9	−5.0	−10	−371	−15	−4.0
7	8	−7	−3.2	−23	−657	−15	−3.1
8	9	−11	−8.7	−32	−1549	−39	−14.5
	16	−22	−17.3	−25	−1219	−28	−10.2
9	14	−11	−7.7	−19	−817	−15	−4.4
	21	−19	−13.2	−38	−1634	−31	−9.4
	28	−23	−15.5	−45	−1931	−41	−12.3
10	16	−11	−7.1	−6	−241	−9	−2.9
	24	−8	−4.9	−10	−404	−13	−4.0
	31	−10	−6.4	−6	−260	−10	−3.2
11	12	−16	−11.7	−31	−1310	−29	−9.3
	19	−16	−11.7	−25	−1045	−29	−9.4
12	22	−6	−3.6	−5	−154	−11	−2.5
13	11	−7	−5.9	−20	−677	−23	−5.8

* Compared with initial determination.

mal relationship is indicated by the diagonal line. It is apparent that in 17 of 22 instances the weight changes were greater than could be accounted for solely on the basis of the sodium changes, whereas, in five instances, the decrease in body weight was less than could be accounted for solely on the basis of a change in exchangeable sodium.

Na^{24} Space. Warner and his co-workers[3] have previously reported that the mean sodium^{24} space in elderly adults with decompensated cardiovascular disease was 41.7 per cent of the body weight. The mean of the initial values obtained in the present series (48.6 ± 2.4 per cent) was slightly higher than that in Warner's series. In all 13 subjects the sodium^{24} space decreased by at least 10 per cent of the original value. The maximum decrease (49 per cent) was observed in case 2.

In most instances the value for Na^{24} space per kilogram tended to decrease during therapy of congestive failure. In 9 of the 13 subjects, the changes in weight were too great to be accounted for solely on the basis of a change in Na^{24} space. This relationship parallels that observed with the exchangeable sodium content.

Serum Sodium Concentration. The initial serum sodium levels were below 135 mEq. per liter in seven subjects. In all of these individuals, subsequent values obtained during therapy of the congestive heart failure were higher. In case 11, the initial value of 131.2 mEq. per liter dropped to 127 mEq. per liter and then rose to 139 mEq. per liter; satisfactory diuresis was obtained at the time the serum sodium concentration was lowest.

Initially normal values decreased to 129.1 mEq. per liter and 123.0 mEq. per liter, respectively, in two subjects (cases 7 and 9) during diuresis; no abnormal clinical symptoms or signs appeared at this time. There was no correlation between the presence of a serum sodium concentration below 135 mEq. per liter and the development of the symptoms and signs of the "low salt syndrome," such as lethargy, weakness, and somnolence.

The changes in serum sodium concentration

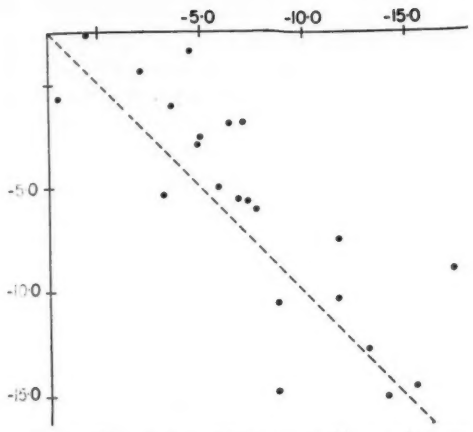


FIG. 1. Correlation of Changes in Na-e and serum Na with changes in body weight during therapy of congestive failure. Abscissa shows change in weight (Kg.); ordinate, $\Delta \frac{\text{Na-e}^*}{(\text{Na})}$.

were unpredictable and could not be correlated with the amount of mercurial diuretic which was given.

Serum Potassium Concentration. Serum potassium concentrations as low as 3.3 and 2.7 mEq. per liter were observed on only two occasions (cases 1 and 3). The value of 3.3 mEq. per liter was observed in case 3 at a time when the patient was responding poorly to treatment and was lethargic and somnolent. A dramatic clinical improvement occurred before the second determination, when the serum potassium concentration had risen to 5.1 mEq. per liter. Diuresis, however, did not occur for another week. The value of 2.7 mEq. per liter was obtained in case 1 during intensive mercurial therapy. This patient became disoriented and somnolent; potassium given orally in small amounts produced dramatic improvement, and he again became alert.

COMMENT

The exchangeable sodium content is a measure of the sodium in the body which is available for exchange with the radioisotopic atom and reflects a functional component of the body rather than an anatomic unit. Although there is some question as to whether this determination measures the total body content of sodium and whether the injected radioactive isotope of sodium ever reaches complete equilibrium with all the native sodium in the body,[6] the values obtained are reproducible and the method is practical for serially following changes in sodium metabolism in the living subject.

The initial values for exchangeable sodium content per kilogram in the present series were higher than those previously reported;[3] this suggests that the subjects in the present study were retaining more sodium. The results indicate that patients with exchangeable sodium contents twice as high as the usual value found in chronically ill, edema-free patients may have normal serum sodium concentrations. Indeed, in several instances, the serum sodium concentration was abnormally low at a time when the total body content of sodium was markedly increased. Clinically, most of the subjects did not attain an edema-free state during the period of observation, and this fact is reflected by the final values for exchangeable sodium content per kilogram, which were higher than those reported in edema-free subjects.

A decrease in body weight which exceeds the relative decrease in exchangeable sodium content and the radiosodium space can be most logically explained on the basis of some alteration within the intracellular compartment or in the non-aqueous tissues of the body, such as body fat. The interpretation that such a decrease in body weight is due to a loss of intracellular fluid is consonant with the conclusion reached by other investigators,[1, 2, 7] using the external balance method.

In five instances the change in exchangeable sodium was greater than the change in total body weight due to loss of extracellular fluid. The most likely explanation of the discrepancy in this direction would be that, at the time of the first measurement, the patients had an abnormally high intracellular sodium content, possibly associated with potassium depletion; with diuresis and the associated improvement in the congestive state, some of this intracellular sodium was replaced with potassium.

In spite of intensive therapy with mercurial

* Change in Na-e corrected for change in serum sodium concentration and expressed in liters.

diuretics, no untoward effects such as somnolence, weakness and disorientation, which have been previously associated with the "low salt syndrome,"[8] were observed concomitantly with a decrease in serum sodium concentration. Such symptoms and signs, in the present study, were noted in two subjects at a time when the serum potassium concentration was decreased; in one of these patients a dramatic improvement occurred when oral supplements of potassium were administered. This observation suggests that some of the adverse side effects of intensive mercurial therapy may be more closely related to a depletion of the body store of potassium than to a depletion of sodium.

Summary

The radioisotope dilution method was used to make serial determinations of the exchangeable sodium content of the body in 13 subjects with congestive failure. The mean value (65.3 ± 3.2 mEq. per kilogram) was considerably higher than in elderly non-edematous subjects (40.6 ± 1.5 mEq. per kilogram). Body weight and exchangeable sodium content decreased with intensive therapy. In most instances the decrease in body weight was too great to be accounted for solely on the basis of the change in radiosodium space or exchangeable sodium content. This weight loss, in excess of the amount which can be explained by the decrease in sodium values, is attributed to loss of intracellular fluid.

Summario in Interlingua

Le methodo del dilution de radioisotopos esseva usate in determinationes serial del contento de natrium excambiabile in le corpore de 13 individuos con dysfunctionamento congestive. Le valor median (65,3 ± 3,2 milliequivalentes per kilogramma) esseva considerabilemente plus alte que in non-edematose individuos de etate avantiate (40,6 ± 1,5 milliequivalentes per kilogramma). Le pesos corporee e le contentos de natrium excambiabile se abassava in le mesura que le therapia esseva intensificate. In le majoritate del casos le reduction del peso corporee esseva plus grande que lo que haberea essite explicabile integremente super le base del alteration del spatio de radionatrium o del contento de natrium excambiabile. Le excesso del perdita de peso—i.e. le perdita de peso non explicabile per le reduction del valores de natrium—es attribuite per nos al perdita de fluido intracellular.

References

[1] Miller, G. E.: Water and electrolyte metabolism in congestive heart failure. Circulation **4:** 270, 1951.

[2] Squires, R. D., Crosley, A. P. and Elkinton, J. R.: The distribution of body fluids in congestive heart failure. III. Exchanges in patients during diuresis. Circulation **4:** 868, 1951.

[3] Warner, G. F., Dobson, E. L., Rodger, C. E., Johnston, M. E. and Pace, N.: The measurement of total "sodium space" and total body sodium in normal individuals and in patients with cardiac edema. Circulation **5:** 915, 1952.

[4] Aikawa, J. K.: Comparison of the thiocyanate and radiosodium spaces in disease states. Am. J. M. Sc. **224:** 632, 1952.

[5] Miller, H. and Wilson, G. M.: The measurement of exchangeable sodium in man using the isotope ^{24}Na. Clin. Sc. **12:** 97, 1953.

[6] Burch, G. E., Ray, C. T. and Threefoot, S. A.: Some theoretic considerations of electrolyte space measured by the tracer method in intact man. J. Lab. & Clin. Med. **42:** 34, 1953.

[7] Iseri, L. T., Boyle, A. J. and Myers, G. B.: Water and electrolyte balance during recovery from severe congestive failure on a 50 milligram sodium diet. Am. Heart J. **40:** 706, 1950.

[8] Schroeder, H. A.: Renal failure associated with low extracellular sodium chloride; Low salt syndrome. J.A.M.A. **141:** 117, 1949.

CLINICAL PROGRESS

EDITOR: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Cardiovascular Manifestations of Collagen Diseases

By MATTHEW TAUBENHAUS, M.D., BERNARD EISENSTEIN, M.D. AND ALFRED PICK, M.D.

THE first descriptions of disease entities, which today are included in the category of "collagen diseases," were made more than a century ago. Through the decades many more entities were described clinically, but until recent years no fundamental common denominator was suspected. Significant contributions which went beyond mere clinical and morphological recognition were made after 1930. The studies of Rich and Gregory,[1] confirming older observations that vascular changes resembling polyangiitis can be produced experimentally by foreign proteins and allergens, have become common knowledge. Much investigative work has been carried out to apply this concept to all the other entities in this category. These attempts have met with success or failure depending on the type of disease investigated. Even more fruitful was the concept proposed by Klemperer and co-workers[2] that these diseases primarily involve the connective tissue structures. The latter then would react like an organ system. Due to the diffuseness of mesenchymal tissue the manifestations would be protean. This important concept provided a great stimulus to research concerning the physiology, histochemistry and physical properties of connective tissues. An intensive search for abnormalities in these respects has been carried out by numerous investigators with the result that many features common to the various diseases were observed. The term "collagen disease" was coined, is in general use, and will be applied in this presentation, although actually there is no justification to assume that the collagen fiber is the only structure involved. Connective tissues consist of cells, fixed and migrating, fibroblasts, mast cells, histiocytes, lymphoid elements and plasma cells. These cells are embedded in a plastic matrix consisting of an amorphous mass and a meshwork of minute fibrils discernible only with the electron microscope. The amorphous element, commonly known as ground substance, is composed of mucopolysaccharides and mucoproteins, the chemistry of which has been recognized to some extent.[3,4,5] Within this matrix larger fibrils are arranged in strands forming fibers. The latter are fairly well defined chemically and physically and are divided into three groups called collagen, reticulum and elastic fibers. The extensive work delineating these structures has been reviewed recently.[6,7] It would appear that the ground substance is elaborated by the connective tissue cells and is in equilibrium with the plasma.[8] The fibers probably originate from the ground substance. Hence it seems impossible for one element to undergo a change without assuming that all the elements must have suffered. Inasmuch as the connective tissue forms an intimate part of the blood vessels and the basement membranes and is present in every organ of the body, by necessity, the function of most organs will be profoundly influenced by the state of the connective tissue. For these reasons, the term collagen disease is

From the Department of Medicine and the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Aided by United States Public Health Grant No. 258(C2).

inadequate. Similar concepts have been clearly expressed by Lyman Duff.[9]

The cardinal pathologic changes occurring in the connective tissue have been repeatedly reviewed.[10] Fibrinoid degeneration, changes in the ground substance and in fiber formation and inflammatory reactions are commonly encountered in all these diseases. It must be clearly stated that in spite of a similarity of the morphologic features, clinically these diseases stand out as separate entities, although overlapping is commonly observed. This will be brought out in the subsequent discussion of the various entities.

Most authors have included rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, necrotizing angiitis, progressive systemic sclerosis (scleroderma), dermatomyositis and serum sickness into the category of the collagen diseases. More recently the addition of thrombotic thrombocytopenic purpura has been suggested. Other diseases have been also associated with a primary derangement of the mesenchyme, however insufficient evidence exists to warrant their inclusion into this group.

The cardiovascular system is involved to a varying degree in all of these diseases. In fact, clinically, cardiovascular manifestations may predominate in some. The purpose of this review is to compile information on such manifestations of collagen diseases and evaluate their significance. Rheumatic fever, uncomplicated rheumatoid arthritis, and thrombotic thrombocytopenic purpura will be omitted from these discussions.

Systemic Lupus Erythematosus

With the accumulation of our knowledge of systemic lupus erythematosus and particularly the advent of a rather specific test, namely the LE cell preparation, it has become apparent that this disorder may actually last for months or years before cardiovascular manifestations become clinically discernible. At autopsy, involvement of the heart and the vessels dominates the picture and the pathological diagnosis is actually made on the basis of these changes. Clinically, the leading signs are fever, weight loss, the more or less typical erythematous skin lesions, lymphadenopathy and splenomegaly, arthralgias or actual arthritis identical with the rheumatoid type, polyserositis, pneumonitis and anemia. Central nervous system manifestations may initiate the syndrome. A false positive serologic test for syphilis, normochromic anemia, leukopenia, thrombocytopenia, hyperglobulinemia and a rapid sedimentation rate are found commonly when laboratory tests are carried out. A positive LE cell preparation is present in about 75 per cent of the cases at one time or another. Any one of the clinical or laboratory findings may antedate the full blown syndrome by years. The entire subject has been recently reviewed.[2, 11, 12, 13, 14]

The pathology of the cardiovascular manifestations briefly is as follows:

(1) The arteries and arterioles of almost any organ of the body may undergo subendothelial fibrinoid necrosis with proliferation of fibroblasts, but relatively little inflammatory reaction. The fibrinoid change can extend throughout the entire vascular wall. Actual occlusion of the lumen by thrombosis is rare but swelling of the vessel wall may cause narrowing of the lumen and impairment of the blood flow. In some organs like the spleen and the kidney, the vascular pathology assumes certain characteristic features. These are sclerosis of the collagen fibers around central and penicilliary arteries of the spleen and the wireloop appearance of the glomerular arterioles. The latter lesions may precede the development of a glomerulonephritis.[15] The generalized arteritis shows features common with other diseases involving connective tissues and their specificity has been challenged.

(2) There is usually involvement of the pericardium and epicardium characterized by fibrinoid necrosis which may involve large portions of these membranes.

(3) The myocardium is involved by a fibrinoid necrosis of the supportive structures and blood vessels leading to secondary degeneration of the muscle fibers and focal fibrosis.

(4) The endocardium may be involved in a similar fashion. Thus, in the valves the degeneration of the ground substance and increase of the fibrinoid material may produce such swelling as to account for actual verrucae.

These verrucae are found on all four valves, most frequently on the tricuspid valve.[16] Severe valvular deformity as seen in rheumatic carditis does not occur. The verrucae occur on both sides of the cusps and in addition, the mural endocardium and the endocardium of the valve pockets are involved. Hematoxylin bodies may be observed in the valves as well as in many other organs.

It is noteworthy that many cases of proven systemic lupus erythematosus have marked functional derangements without adequate pathologic substrate at necrospy. This would indicate that the normal physiologic responses to the vascular bed and connective tissues may be profoundly altered before any histologic change can be detected. Such an assumption is corroborated by plethysmographic studies of the circulation in the fingers[17] and studies with the aid of a capillary microscope.[18]

The clinical manifestations due to arteritis are protean. Raynaud's phenomenon is not uncommon and has been observed in as high as 26 per cent of the cases in one series.[13] Central nervous system involvement caused by the vascular pathology occurs, and convulsions may initiate a more generalized clinical symptomatology. Hemiplegia and peripheral neuritis on this basis have also been observed. Retinal hemorrhages and exudates may be due to local angiitis as well as secondary to hypertension. Gastrointestinal hemorrhages have been described and even pancreatitis due to lupus angiitis has been observed.[13] Renal vascular involvement manifested by albuminuria, microscopic hematuria and cylinduria of the various types occurs in about two-thirds of the cases. Hypertension due to lupus nephritis is seen usually when the renal involvement is severe enough to lead to azotemia. Muscle biopsy is of little aid in demonstrating vascular lesions.

Arteritic lesions of the myocardial vessels may lead to the picture of myocardial infarction. Two such cases were observed by us and the electrocardiogram of one (fig. 1) illustrates this. Both of these cases exhibited anginal pain as one of the outstanding clinical manifestations.

Pericarditis with all its characteristic signs and symptoms is one of the most common of the cardiac manifestations. It has been reported in as high as 45 per cent of cases in one series.[13] At times, effusion has been so massive as to require pericardiocentesis to relieve cardiac

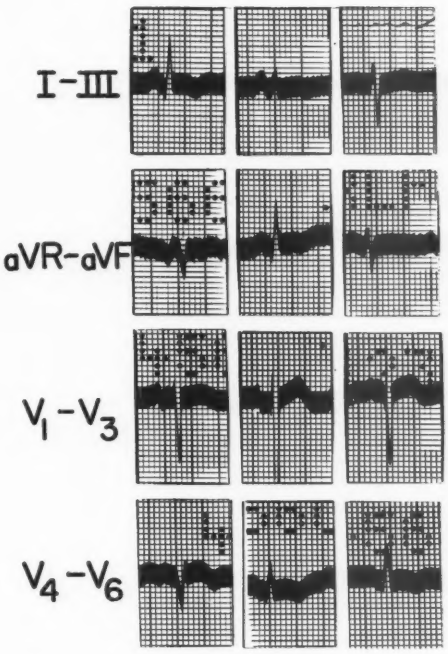


FIG. 1. *A 53 Year Old Female with Systemic Lupus Erythematosus and Anterior Wall Necrosis.* Two episodes of "viral" pneumonia occurred 9 and 8 months before admission. Three months later, she was admitted to another hospital for severe substernal pain. The electrocardiogram at this time showed a typical pattern of recent anterior wall infarction complicated by pericarditis. Subsequently she had recurrent fever, chest and shoulder pain. Blood pressure was 100/65 mm. Hg. The heart was enlarged, a pericardial friction rub and gallop rhythm were present. LE preparation was positive. There was an initial response to cortisone. She died 14 months later in shock, subsequent to another episode of severe chest pain. No autopsy was obtained.

The electrocardiogram shown, obtained five months after the first attack of chest pain and one week after admission, reveals the characteristic features of injury, ischemia and circumscribed necrosis on the anterior wall consisting, respectively, in elevation of S-T in leads I, aV_L, V_3 and V_4, inversion of T in lead I and leads V_3 through V_6, and QS complexes in leads V_3 and V_4.

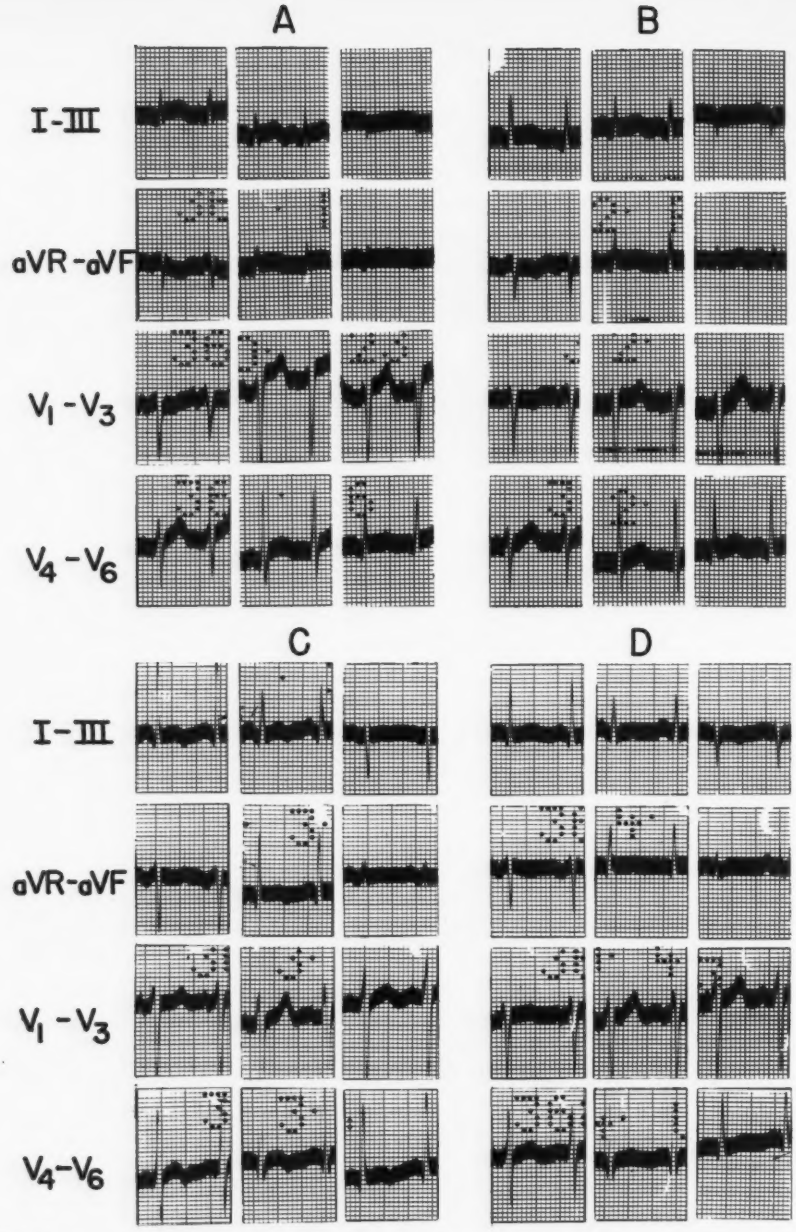


FIG. 2. *Acute Pericarditis in a 35 Year-Old Male with Systemic Lupus Erythematosus.* History of intermittent swelling and tenderness of the joints for seven years. He was admitted for fever, weight loss and joint pain. Blood pressure was 110/80 mm. Hg. The heart was enlarged, a pericardial friction rub was present, as well as bilateral pleural effusions. Urine showed 3 plus protein, red blood cells and casts. Blood urea nitrogen was 60 mg. per 100 cc. Bone marrow was positive for LE cells. A favorable response to corticotropin occurred. No clinical relapse was present for three years; proteinuria persisted while BUN stayed around 20 mg. per 100 cc.

The electrocardiogram at first showed (record A) a sinus tachycardia, low voltage in the limb leads, and S-T deviations in both limb and precordial leads. These subsided within four days (record B). Four weeks later (record C), while QRS increased in amplitude, flat inverted T waves developed in the limb leads and the left precordial leads, with partial restitution to low upright T waves within the next two weeks (record D). Thus, although one of the characteristic features of diffuse pericarditis, namely initial concordancy of the S-T deviations is not seen, the diagnosis of pericarditis could be based on the typical protracted evolution of T wave alterations in the absence of significant QRS changes.

tamponade. In any female who presents herself with the findings of pericarditis, the diagnosis of systemic lupus erythematosus has to be seriously considered. Lupus endocarditis, as first observed by Libman and Sacks, is found in about 40 per cent of the cases at necropsy, although it is usually clinically silent. Systolic murmurs are frequent, but difficult to evaluate in view of the common occurrence of fever, tachycardia and anemia. Mitral and aortic diastolic murmurs have been observed and attributed to the verrucous endocarditis. Engrafted upon these, bacterial endocarditis may occur.[19] Cardiac enlargement without pericardial effusion is well known and can be attributed to the myocardial involvement described above. Congestive failure may occur in as high as 24 per cent of the cases.[11]

The histologic alterations of the myocardium developing in the course of systemic lupus erythematosus are reflected in the electrocardiogram when cases are followed in serial tracings. In accordance with the incidence of the clinical manifestations of cardiac involvement, most often changes are attributable to an acute diffuse pericarditis, although the electrocardiographic evolution may not always follow the typical course. Discordant S-T

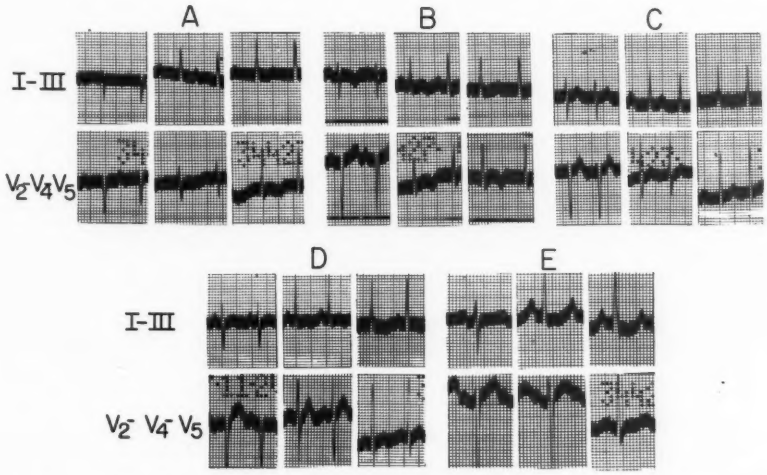


FIG. 3. *Myocarditis in the Course of Systemic Lupus Erythematosus (SLE) in a 16-Year-Old Girl.* The patient had a history of recurrent right upper quadrant pain for two years. She was admitted for fever, arthralgia and swelling of hands. Blood pressure was 105/90 mm. Hg. There was a typical butterfly rash of face. The heart was not enlarged. A loud systolic apical murmur and gallop rhythm were present. Hepatosplenomegaly and generalized lymphadenopathy were also found. The total plasma protein was 9 Gm. per 100 cc, and globulin, 5.7 Gm. per 100 cc. The Kahn was positive. Muscle and lymph node biopsy was suggestive of systemic lupus. The patient responded to corticotropin therapy, in the course of which transient hypopotassemia developed. At present she is clinically well, being maintained in this state by small doses of cortisone.

The electrocardiogram shows sinus tachycardia, a variable P-R interval and ST-T alterations in different leads of the consecutive tracings. In record A, P-R measures 0.32 second., with P superimposed on apparently flat T waves. In record B, 12 days later, P-R has returned to normal, (0.14 second) while T has become inverted in leads I, II, V_4 and V_5. After 16 days (record C), P-R appears prolonged (0.24 second) once more, and T, though in part distorted by the superimposed P wave, is upright in all leads except lead III. In record D, four weeks later, the P-R has returned to normal while additional T-wave inversions have developed in leads II and V_5. The last tracing (record E), three weeks later, shows S-T depression in leads II and III, and flat, diphasic T waves in the limb leads and lead V_5. The electrocardiographic diagnosis of myocarditis is based on the *persistence* and protean nature of the electrocardiographic alterations, involving A-V conduction and the ST-T configuration. In record E these alterations appear to be modified by the effects of hypopotassemia.

deviations in the initial stages, as seen in figure 2, may be due to a circumscribed localized affection of the epicardium by the pathologic process before a diffuse pericarditis develops. Transient T-wave flattening and inversion in the various leads, associated with intermittent P-R prolongation and with periods of restitution in between (fig. 3), would suggest multiple areas of myocarditis in different stages of evolution and reparation, side by side. However, development of large and circumscribed areas of necrosis are sometimes indicated by the finding of a classical infarct pattern with typical QRS and ST-T deformation (fig. 1). When the myocardial involvement is less extensive, or no serial tracings are available, the electrocardiogram may be normal, or show merely T-wave flattening of a nonspecific type.

In summary, systemic lupus erythematosus represents the effects of extensive ground substance involvement in serous and synovial membranes, endocardium, myocardium and vessel walls. Many of the clinical manifestations overlap with signs of rheumatic fever, rheumatoid arthritis and necrotizing angiitis. Positive LE cell preparations have helped considerably in the identification of the disease.

Necrotizing Angiitis

Since the original description of periarteritis nodosa by Kussmaul and Maier in 1866, an extensive literature has arisen which attempted to unify the bizarre and apparently unrelated multiple organ involvement in terms of a disseminated vascular lesion. Since Rich and Gregory[1] in 1942 experimentally produced this disease by sensitization of animals with foreign proteins and ascribed it to hyperergic reactions in the arterial wall, attempts have been made to apply this concept to man. On the other hand, certain entities have been delineated which permitted an early differentiation of periarteritis into clinical and pathologic groups. Friedberg and Gross[20] have observed the frequent association with rheumatic heart disease. Horton and coworkers[21] have separated a different type, namely temporal arteritis, which was singularly characterized by its course, distribution and pathology. Only recently Zeek[22] contributed to a clarification of the diverse pathologic clinical picture by emphasizing that necrotizing angiitis is not a uniform disease. According to her studies there are at least five different groups, more or less sharply defined, into which the majority of these conditions would fall. These are: (1) hypersensitivity angiitis, (2) allergic granulomatous angiitis, (3) rheumatic arteritis, (4) periarteritis nodosa and (5) temporal arteritis.

The term necrotizing angiitis is applied to the lesion which is common to all these groups. It consists of focal fibrinoid necrosis and inflammatory reaction in the vessel wall. Arteries and veins of any caliber may be involved. In the *hypersensitivity angiitis*, which occurs in response to foreign protein and drugs, such as sulfonamides, small arteries, arterioles, venules and capillaries are affected. The most common sites of the process are the kidneys and the heart. In contrast to periarteritis, involvement of the pulmonary vessels and splenic follicular arterioles is also common. The lesions appear usually to be of the same age. They start as a fibrinoid necrosis in the subendothelial ground substance, spreading towards the periphery and accompanied by cellular infiltration of the vascular wall and the surrounding tissues. Eosinophils are commonly present. Necrotizing glomerulitis is a frequent finding.

Hypersensitivity angiitis is difficult to diagnose clinically because of its frequent association with other diseases, for which the sensitizing agent was given. Aside from foreign proteins and sulfonamides, other drugs, such as propylthiouracil, iodine and dilantin, have caused the vascular reaction. The course is rapid and frequently fatal. Inasmuch as the diagnosis is usually made at necropsy, it is difficult to say whether milder forms with reversible lesions occur. The arteries of the skeletal muscles are usually not involved, and muscle biopsy is usually of little diagnostic help. Fever is always present and petechial and urticarial rashes are frequent. Nephritis with hematuria and azotemia is the prominent feature. Cardiac manifestations such as congestive failure occur and may be due to multiple miliary infarcts in the myocardium.

The *allergic granulomatous angiitis* as described by Churg and Strauss[23] is associated with asthma and eosinophilia. Extravascular lesions occur consisting of nodular granulomata with giant cell production and fibrinoid collagen degeneration in the nodules. The distribution of the vascular lesions resembles that seen in hypersensitivity angiitis. However, here, the lesions are of various ages and there is more abundant eosinophilic infiltration. In addition involvement of the mesenteric vessels with aneurysm formation is common.

Clinically, the allergic granulomatous type of necrotizing angiitis is characterized by the appearance of multiple organ system involvement, resulting from vascular occlusion and subsequent infarction in individuals who have previously demonstrated asthma, fever and eosinophilia. Peripheral neuropathy, hypertension, and azotemia are common. Skin involvement consisting of subcutaneous nodules affords biopsy verification of the diagnosis of allergic granuloma. Death is usually due to cardiac failure, cerebral hemorrhage or uremia.

Arteritis occurring in association with rheumatic fever and carditis (*rheumatic arteritis*) has been studied by Friedberg and Gross.[20] Small arteries and occasional veins are involved and the lung and heart are common sites of the lesions. Mesenteric vessels are also affected, but less commonly so. Aschoff bodies are seen in the myocardium and characteristic valvular lesions occur.

The clinical picture of rheumatic angiitis is dominated by the course of a fulminating rheumatic fever. Apart from the pancarditis and the joint manifestations, certain features will lead to the consideration of a generalized vascular involvement. Abdominal pain, at times severe enough to lead to laparotomy, has been described in this entity due to arteritis of the mesenteric vessels. Renal involvement with albuminuria and hematuria may occur.

True *periarteritis nodosa* is the most common form of necrotizing angiitis. The small and medium sized arteries (coronary, mesenteric, renal and muscular) are most commonly involved. The splenic follicular arterioles and pulmonary vessels are usually spared. The coronary arteries rank next to the renal vessels in frequency of involvement. The lesions appear in various stages of development. Aneurysm formation is quite characteristic and due to weakening of the vascular wall. Histologic evidence of myocardial infarction has been described in about 17 per cent of cases, which is second only in frequency to infarction of the kidney. Involvement of the coronary arteries without infarction is even more common.[24] Aneurysms of the coronary arteries with rupture and formation of hemopericardium have been described.[25] Rupture of a papillary muscle due to infarction has been observed.[26] Localized involvement of the pulmonary arteries has been described with severe pulmonary hypertension as seen in congenital heart disease.[22]

True periarteritis nodosa has protean manifestations because of the extensive organ involvement secondary to the vascular disease. Focal ischemia of smaller or larger areas caused by arterial occlusion may occur in any organ of the body. Thus thrombosis of the cutaneous arteries may lead to ulceration of the skin; involvement of arteries to the skeletal muscles will lead to muscle pain and tenderness; peripheral neuritis will be a result of arteritis of the nutrient arteries of the nerve; involvement of the mesenteric vessels may lead to bleeding in the gastrointestinal tract and may mimic an active peptic ulcer. As can be seen by these examples, the possibilities are unlimited. Cardiac enlargement, retinopathy, and partly also congestive failure are secondary to hypertension and renal involvement. Raynaud's phenomenon, so commonly observed in systemic lupus erythematosus, dermatomyositis and scleroderma occurs rarely in periarteritis. Congestive failure is the most common cause of death. Other causes are uremia and cerebrovascular accidents. Serial electrocardiographic tracings may show a more or less typical evolution of pericarditis, myocarditis or confluent myocardial necrosis. In others, electrocardiographic alterations may fail to take a typical course in serial tracings and consist in a variety of recurring and quickly subsiding changes of ST-T and/or P-R, or reduction of voltage (fig. 4). When hypertension and renal involvement dominate the

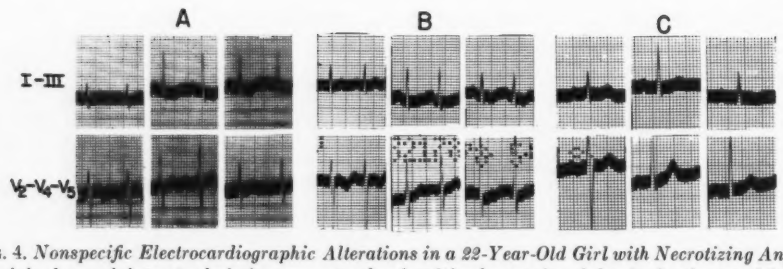


FIG. 4. *Nonspecific Electrocardiographic Alterations in a 22-Year-Old Girl with Necrotizing Angiitis.* The original complaints at admission were cough, pleuritic chest pain, abdominal pain, vomiting and arthralgia. During three and one-half years of observation the following findings were intermittently noted: recurrent pneumonitis and hemorrhagic pleural effusions, pericardial friction rub, a harsh systolic apical murmur, and gallop rhythm. At the time of the last examination, an aortic diastolic murmur had developed. Blood pressure was always normal. Persistent 2 plus to 3 plus proteinuria, microhematuria and anemia were present. Muscle biopsy revealed periarteritis. The response to corticotropin and cortisone was only fair, with exacerbations requiring repeated hospitalization. No follow-up was possible since 1952.

The three tracings shown are representative examples of the variety of frequently recurring and rapidly subsiding alterations observed in this patient over a period of four years in 28 electrocardiograms. In record A, the T waves are flat throughout and inverted in leads II, III and V_2. In record B, the T wave is small and upright in lead I, indiscernible in lead II, more inverted in lead V_2; and in lead V_5, S-T is depressed and T is small and diphasic. In record C, the ventricular complexes have a normal configuration but the P-R has lengthened to 0.20 second. While myocardial involvement in the course of the vascular disease seems certain the type of lesions could not be specified as in figures 1, 2 and 3, due to the lack of development of a definite pattern and the frequent periods of restitution between abnormal tracings.

clinical picture, the electrocardiogram will show the usual pattern of chronic left heart strain, or one modified by the associated disturbance of the electrolyte balance. The electrocardiogram, while reflecting the involvement of the myocardium by the systemic disease, does not provide means to differentiate the various collagen diseases.

Temporal arteritis seems to be usually restricted to the cranial arteries, although Harrison[27] in reviewing the literature on this subject has described evidence of dissemination. Histologically, the lesion is characterized by predominance of nodules of granulomatous inflammation surrounded by inflammatory cells and foreign body giant cells. Associated with this is the fibrinoid necrosis in the involved vessel wall.

The clinical manifestations of cranial arteritis have been extensively reviewed by the same author. It is singular in that older individuals are affected. The larger muscular arteries are involved proximal to their bifurcation and the aorta as well as smaller vessels may be the site of the characteristic microscopic lesion. However, the principal signs and symptoms are referable to the cranial arteries. Noteworthy is the frequent occurrence of blindness. Death occasionally occurs as a result of extensive cerebral involvement, but in one case, death was due to myocardial infarction secondary to coronary arteritis of this type.[28] Usually the course is benign and self limited.

The recognition of these various pathologic types of necrotizing angiitis would seem to permit the delineation of clinical syndromes corresponding to the histological lesions. However, many cases are encountered which are difficult to place in any of these categories. Overlapping of various types of angiitis and their coexistence with manifestations of other collagen diseases make sharp definition impractical.

In general, necrotizing angiitis is a primary disease of the vessel wall. Other mesenchymal structures are involved to a lesser degree. The functional impairment of organs is dependent on the diminution of blood flow by narrowing of arterial lumina. Only a few features, such

as pleuritis, pericarditis, synovitis and myocarditis, may not be adequately explained by local ischemia and infarction. We have to assume that the same etiologic factor, which leads to the arterial lesions, attacks serous membranes and interstitial tissues of the myocardium and produces a generalized extravascular reaction. Similarly polyarthritis, resembling the rheumatoid type and occurring in conjunction with polyangiitis, cannot be explained by the arterial lesion. Such reactions, though, play a relatively small role in the total pattern.

Progressive Systemic Sclerosis (Scleroderma)

Generalized increase of collagen fibers is the outstanding manifestation of progressive systemic sclerosis. Thickening and characteristic appearance of the skin of the face, extremities and the trunk with limitation of motion due to loss of elasticity are prominent. Involvement of the esophagus is common and leads to changes in the shape and the function of this organ which are of great diagnostic importance. The small bowel is involved occasionally and the colon rarely. Involvement of the joints may simulate rheumatoid arthritis. Atrophy of the skeletal muscles is frequent and interstitial changes are seen which at times may resemble the lesion in dermatomyositis. Pulmonary involvement is very common and important for the understanding of the genesis of one aspect of the cardiac lesion. The fibrosis involves the peribronchial and alveolar interstitium with thickening and actual destruction of the alveolar walls leading to cyst formation. There may be extensive obliteration of capillaries and alveolar spaces.[28a] Secondary infections lead to chronic endobronchial disease. No characteristic laboratory findings have been reported. Several reviews on this subject have been published recently.[29, 30, 31]

Vascular manifestations are extensive and play an important role in the pathologic and clinical picture. The histologic changes have been aptly summarized.[31] There is thickening of the vessel wall by perivascular fibrosis and infiltration of the adventitia with polymorphonuclear and round cells. Intimal proliferation occurs and may lead to vascular occlusion. Usually smaller vessels are affected, but lesions of a similar type may be encountered in any artery of the body. Such vascular changes may be observed in the skin and along with the changes of the collagen, elastic fibers and epidermis, represent the criteria for the diagnosis of scleroderma. Extensive vascular changes may be encountered in the kidneys which seem to be quite characteristic. According to Moore and Sheehan[32] the initial lesion is a thickening of the intima of the intralobular arteries leading to a gradual ischemic atrophy of portions of the renal cortex. Subsequent fibrinoid necrosis of the distal part of the intralobular arteries and of the afferent arterioles occurs. Fibrosis of the glomeruli may follow.

Clinical manifestations of the vascular involvement are quite prominent. Raynaud's phenomenon is prevalent, occurs in a high percentage of cases and may lead to trophic changes of the fingertips with necrosis. Renal manifestations of the vascular involvement are dependent on the extent of the lesions and may vary from albuminuria to severe renal failure and terminal hypertension. Until a late stage of the disease is reached, renal involvement is not apparent clinically. Pulmonary involvement will manifest itself in the following manner: The alveolar-capillary block secondary to alveolar fibrosis and vascular obliteration will result in an impairment of gas exchange leading to hypoxia and carbon dioxide retention. Decrease of pulmonary elasticity and emphysema have already impaired the efficiency of pulmonary ventilation. Reduction in the pulmonary artery vascular bed leads to pulmonary hypertension and this is accentuated by hypoxia. In protracted cases a resulting polycythemia may add to the pulmonary artery pressure and strain on the right heart.[33, 34] Clinical manifestations in other organs may occur as a result of vascular changes. However, in view of the extensive alterations of the collagen seen in progressive systemic sclerosis, it may be difficult to ascribe these manifestations to vascular changes alone in any given case.

Cardiac involvement in progressive systemic sclerosis has been recognized more frequently

since Weiss and associates[35] called attention to these lesions. It is important to note that three of the cases described by these authors presented cardiac failure as much as two years prior to the onset of the cutaneous pathology. This has also been noted by Goetz.[36] Review of such autopsied cases seems to indicate that the weight of the heart was moderately increased in about one-half of the cases. Selective hypertrophy and dilatation of the right heart may occur due to the pulmonary lesions. Pericardial and pleural effusion, when it occurs, is secondary to congestive failure. Pleural and pericardial thickening is frequent. Primary changes in the myocardium are outstanding. They consist apart from the involvement of the myocardial vessels, which has been described above, in interstitial fibrosis which occurs in patchy distribution and is independent of any vascular impairment. Goetz[36] deduces from his observations on three cases that various stages of the interstitial myocardial fibrosis can be differentiated. Initially, hyperemia and then a very vascular, young connective tissue may separate the muscle fibers. Finally, denser fibrosis ensues. The muscle fibers disintegrate as a result of these connective tissue changes and may eventually be replaced by scars. There seems to be no primary involvement of the muscle fibers. Extension of the fibrosis to the epicardium and endocardium occur to a lesser degree. Nodules have been observed at the free margins of the mitral and tricuspid valves. The significance of such rheumatic stigmata in the valves is, however, questionable.

The clinical manifestations of heart disease in progressive systemic sclerosis are fully explained by the pathological findings. Involvement of the small myocardial vessels is rarely extensive and secondary local ischemia plays a minor role. The major clinical signs result from the interstitial fibrosis and the degeneration of the myocardial fibers. The pattern of the fibrosis will greatly determine the actual clinical findings. If the extent of the fibrosis is great and diffuse, myocardial failure will ensue. If the fibrosis is focal, isolated myocardial damage may be reflected in conduction defects recognizable only electrocardiographically. The altered dynamics of the pulmonary circulation resulting from alveolar-capillary block may also contribute to the circulatory embarrassment. Precordial pain may occur but it is not of an anginal nature. Congestive failure may be a prominent feature of progressive systemic sclerosis. The manifestations are not different from heart failure due to any other myocardial disease. However, dyspnea may be more difficult to interpret because of the coexisting involvement of the lungs, the chest wall and the diaphragm. Cyanosis on a cardiac basis may have to be differentiated from that due to pulmonary insufficiency and to local vascular changes, as seen in Raynaud's syndrome. Pulmonary rales may be due to passive hyperemia and also to bronchial disease. Paroxysmal nocturnal dyspnea and orthopnea will point to a cardiac origin. Edema is very common and may be found in the absence of congestive failure. In severe cases, generalized anasarca occurs with effusions in the serous cavities. Isolated right heart failure has been observed.[37] Accentuation of the pulmonary second sound and diastolic gallop are present in a high percentage of the cases exhibiting congestive failure. Diastolic murmurs do not occur unless there is valvular disease of other origin. Systolic murmurs along the base or at the apex are common, but are usually of grade 1 to 2 intensity. Pericardial friction rubs have been described. The blood pressure is not elevated unless hypertension of other origin or major renal involvement is present. Cardiac catheterization has been performed and has revealed an elevated pulmonary artery pressure.[38] Angiocardiography has been used[37] and enlargement of the pulmonary arteries and right ventricle demonstrated. The configuration of the heart as seen roentgenologically is characterized in the typical case by a triangular shape with poor pulsation suggestive of pericardial effusion. This has led to unsuccessful attempts at pericardiocentesis. A review of the X-ray findings[39] has shown that cardiac enlargement is not uncommon even in the absence of failure.

Electrocardiographic alterations will also depend on the extent and the location of the myocardial pathology, the degree of pulmonary

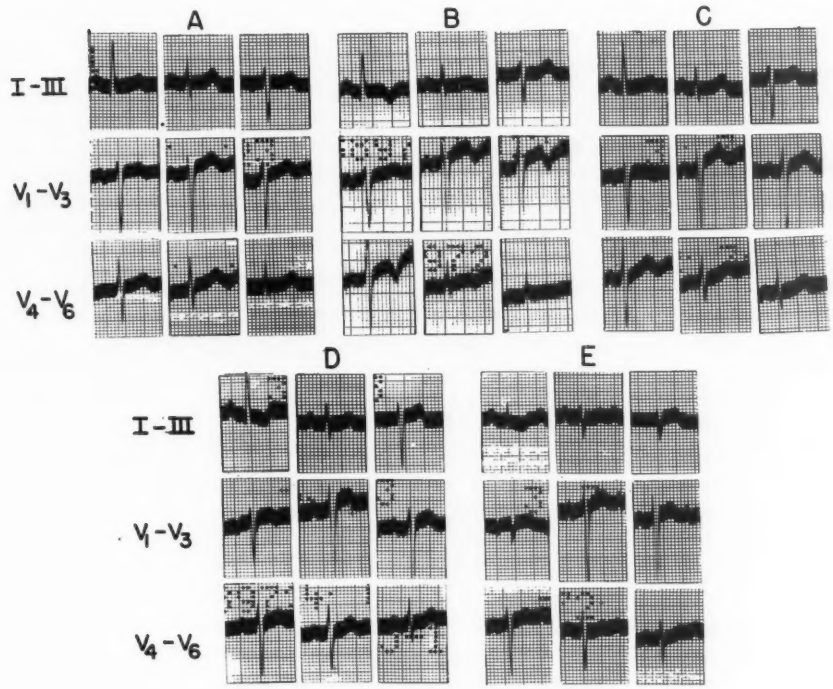


FIG. 5. *The Course of Electrocardiographic Alteration in a 56-Year-old Negro Woman with Progressive Systemic Sclerosis.* There was a nine-year history of progressive thickening of skin of the hands, difficulty in opening the mouth, muscle weakness and a 30-lb. weight loss. She was on digitalis therapy for three years, and cortisone therapy for one and one-half years prior to admission. Blood pressure was 120/58 mm. Hg. The heart was enlarged and gallop rhythm was present, as well as 4 plus edema of the legs. The skin changes were characteristic of scleroderma. The X-ray films showed pulmonary fibrosis. There was a poor response to digitalis and diuretics as well as to cortisone. She died in heart failure with the clinical diagnosis of chronic cor pulmonale.

Autopsy showed scleroderma involving the skin, heart, lung, esophagus, thyroid, and striated muscle. There was hypertrophy and dilatation of the heart, predominantly right sided. Pulmonary arterial ahterosclerosis was present, predominantly in secondary and tertiary branches. Microscopically, there was cloudy swelling of the myocardial fibers with interstitial edema and fibrosis. Thickening and fibrinoid degeneration of the walls of the small coronary arteries, of the epicardium and endocardium was seen.

The first electrocardiogram (record A), taken 16 months before death, is normal in every respect. Record B, taken eight months later, shows an abnormal S-T elevation in lead I and inversion of T in lead I and leads V_2 to V_5, suggesting a lesion on the anterior wall not associated with complete destruction of a large area of the myocardium. Four weeks later (record C), these alterations disappeared, but there is a shift to the left of the transition zone in the precordial leads. Record D, obtained six weeks later, shows an abnormal contour of ST-T in lead I suggesting the development of left heart strain. In record E, taken after four more months, this ST-T contour in lead I is still present while the amplitude of QRS is markedly reduced in leads I, II and III; in lead B_1, QRS has become small and notched in contrast to the large rS complex in lead V_2, and the deepening of S in lead V_6. This suggests the development of right heart strain in addition to left heart strain. The series of electrocardiograms and their evolution gives an idea of the sequence of the development of pathologic findings revealed at autopsy.

involvement and subsequent pulmonary hypertension. Focal fibrosis of the ventricular myocardium may result in non-specific ST-T alterations or prolongation of A-V and intraventricular conduction time. The intraventricular block is usually right sided and this may be related to the concomitant pulmonary disease. An electrocardiogram changed in this way may be the only manifestation of involvement of the heart by the disease. In addition, low voltage and various disturbances of cardiac rhythms, like atrial fibrillation and flutter or tachycardia, have been described. In advanced cases with more extensive systemic involvement, massive replacement of the myocardium by connective tissues, patterns of heart strain and of myocardial infarction can be observed. In figure 5 the progressive character of the disease and the sequence of organ involvement seem to be brought out by the sequence of alterations in serial electrocardiograms.

The degeneration of myocardial fibers explains the transitory benefit of the usual cardiac therapy when failure occurs. Pulmonary complications present a further obstacle to effective management. The course is progressively downhill.

In summary, the outstanding pathology in progressive systemic sclerosis involves excessive formation of collagen which replaces vast areas of the connective tissues. This characterizes the disease clinically. Parallel with this change, extensive vascular manifestations occur which often play a major role in the clinical picture. Inasmuch as both phases of this condition occur simultaneously it is difficult to recognize which one, the vascular or the sclerotic component, occurs first. However, the extent of the sclerosis in certain areas is of such degree that it cannot be accounted for by the accompanying vascular involvement which may be minimal. Similar considerations apply to the myocardium in which the sclerosis may actually replace the cardiac muscle. The involvement of the myocardial arteries and arterioles is of minor importance. Certain similarities exist clinically and pathologically between this condition and dermatomyositis. Even histologic patterns may be very similar. The main lead to the differentiation of both these conditions will be the extensive collagen changes in progressive systemic sclerosis versus the skeletal muscle involvement in dermatomyositis. Although both alterations may occur in either one of the diseases, the extent and the degree will be the determining factor in the differentiation of the two.

Dermatomyositis

Skeletal muscle and skin involvement are the dominating clinical manifestations of dermatomyositis. Muscular weakness in the shoulder and pelvic girdle and extremities with tenderness and swelling are common presenting features. Involvement of the muscles of deglutition gives rise to dysphagia in a significant number of cases. Involvement of the respiratory musculature may cause dyspnea. The picture in the absence of skin lesions may actually simulate muscular dystrophies. The typical skin manifestations consist in periorbital swelling with characteristic heliotrope discoloration. Dermatitis and edema may occur on the trunk and extremities and be unrelated to muscle swelling and tenderness. Fever may occur, but is not always present. No characteristic hematologic or biochemical findings are present. Urinary abnormalities are uncommon and non-specific.

The usual cause of death is pneumonia or respiratory failure secondary to the involvement of the muscles of deglutition and respiration. Complete recovery may occur, but more common is remission with residual muscle atrophy and joint contractures. Malignant neoplasms have frequently been reported in association with dermatomyositis and in one series was seen in 18 per cent of cases.[40] The significance of this is not known. The clinical and pathological features of dermatomyositis have been extensively reviewed.[41, 42, 43, 44]

Vascular changes consist in fibrinoid necrosis and deposition of hyalinized material in the media of the arterioles.[45, 46] Occasionally, deposits within the vascular lumen, suggesting platelet clusters, are also seen. In a case observed by us, platelet thrombi were seen in small myocardial vessels. Inflammatory reactions of the vessels are scanty but vascular

occlusion can occur. These latter changes have been described in the arterioles of small caliber supplying the striated muscles, the myocardium and the submucosal vessels of the esophagus, small intestine and rectum. In rare cases these vascular changes have led to necrosis and ulceration in the intestine with bleeding. The same vascular changes have been observed in the peri-adrenal fat.[44] Histologic alterations have been described in all the elements of myocardium. The muscle fibers show fragmentation, loss of striation and vacuolization. The nuclei are irregular in size and shape. These changes may be focal or more diffuse. The interstitial tissue shows swelling, edema, and occasionally inflammatory infiltrates. The small vessels may show involvement as described above. The epicardium may contain some dense staining collagen. The myocardial changes actually resemble the changes in the skeletal muscle but are less severe. Pericarditis is rare but in one case, observed by O'Leary, subacute mitral endocarditis and obliterative pericarditis, without the presence of Aschoff nodules, was found.[42]

Clinically the vascular manifestations are not very prominent, except for Raynaud's phenomenon, indicating that functional as well as pathologic changes must be present in the arterioles of the finger tips. This manifestation has been observed in about 10 to 25 per cent of the cases of dermatomyositis described and may lead to ulceration of the fingers. Characteristic renal changes have not been observed and no increased incidence of hypertension has been found. Retinopathy consisting of exudate and hemorrhages with cytoid bodies has been reported. These changes are nonspecific but similar to those seen in systemic lupus erythematosus. Occasional infarction of the striated muscle has been described but this is uncommon and not significant in terms of the basic muscle pathology.[46]

The most common cardiac manifestation is tachycardia out of proportion to the temperature elevation.[47] The electrocardiogram may be normal, or may reveal non-specific alterations consisting in S-T depressions and flat or inverted T waves in the various leads without assuming a definite pattern of evolution. Disturbances of impulse formation (auricular fibrillation or auricular tachycardia) and of impulse conduction (S-A and A-V block) have been observed on occasion. Enlargement of the heart is not common although O'Leary and Waisman noted five instances in their series.[42] The blood pressure is usually normal. Blowing systolic murmurs may be heard but in the absence of valvulitis. Congestive failure has been reported but is uncommon. Dyspnea is usually due to involvement of respiratory muscles. In brief, findings other than tachycardia and electrocardiographic abnormalities are uncommon, despite the frequency of myocardial involvement.

In summary, dermatomyositis constitutes a process in which the lesion of the skeletal muscle and the skin predominates. However, involvement of the general mesenchymal structures and disseminated vascular as well as myocardial lesions are also important features of the disease. The general muscular degeneration is not the result of the vascular process. It appears that in this disease the muscle as well as the connective tissues react to some causative factor, which remains unknown. Although dermatomyositis is a clinical entity, overlapping, particularly with progressive systemic sclerosis, exists. The resemblance to systemic lupus erythematosus is superficial.

The Serum Sickness Syndrome

Serum sickness and related reactions due to other foreign proteins have been included in discussions of collagen diseases. Generalized involvement of the mesenchyme and in particular of the cardiovascular apparatus was found to follow massive injections of these agents. The experimental pathology of such lesions has been studied by Ehrich.[10] Serum is less frequently employed in clinical medicine today, but penicillin produces a syndrome similar to that caused by heterologous protein.

Serum sickness is characterized by sudden onset after a latency period of varying duration following the administration of the antigen. Urticaria, joint swelling and fever are the most prominent signs. In contrast to the other collagen diseases, it is characterized by a rather

short, self-limited course with no apparent residuals. Deaths, however, have been reported.

The pathology in the autopsied cases reveals chiefly edema and proliferation of fibroblasts, endothelial cells, plasma cells and lymphocytes in the endocardium, myocardium, pericardium and in the intima and adventitia of arteries and veins. Necrosis of the vessel wall with fibrinoid degeneration has also been described.[48] Clinically, in the milder cases of serum sickness, no cardiovascular manifestations are apparent, except that the urticaria indicates increased vascular permeability. In more severe cases pericardial friction rubs and effusions have been observed.[49] Cardiac enlargement and changing loud systolic murmurs have also been reported.

Electrocardiographic abnormalities in serum sickness may be insignificant or conspicuous. Cases are on record in which T-wave inversions in limb and precordial leads appeared in the acute stage. Several showed S-T deviations and in some instances the appearance of prominent Q waves in the limb leads, or of QS complexes in the chest leads suggested development of myocardial infarction, which actually could be demonstrated at autopsy. Similarly, in penicillin reactions inversion of T waves in the chest leads and patterns of coronary occlusion were seen. The electrocardiographic aspects of serum sickness and related allergic disorders were recently summarized;[50] the material at Michael Reese Hospital was found to be in keeping with these observations.[51]

The manifestations of serum sickness are supposed to be related to antibody formation and its reaction with the antigen, similar to the Arthus phenomenon. Inasmuch as the histologic appearance of the vessels may be indistinguishable from the hypersensitivity angiitis, as described before, the question arises whether the syndrome of serum sickness should be separated from the picture of necrotizing angiitis. Clinically such a differentiation is justified because the course of these two entities usually is divergent.

The Action of Corticotropin (ACTH) and Corticosteroids upon Cardiovascular Manifestations of Collagen Diseases

The advent of corticotropin and corticosteroid hormones has for the first time offered a therapeutic approach to the diseases under discussion. It may be stated at the outset that no curative effect has been obtained with these agents and that therapy is directed to the suppression of certain manifestations of the disease process until a remission may ensue. No attempt will be made in this review to discuss the present knowledge of the basic mechanism of action which is still incompletely understood.

The usefulness of these agents in systemic lupus erythematosus has been repeatedly pointed out by Soffer and co-workers.[52] and their effects have been recently reviewed by Harvey and associates.[14] The beneficial action upon fever, arthralgias and mucocutaneous manifestations and the partial or complete reversal of abnormalities observed by laboratory methods are undisputed. The limiting factor in therapy seems to be the state of the renal lesion. The latter will usually show no response if the disease has progressed to the stage of azotemia. Treatment may even result in an increase in nitrogen retention and albuminuria. The appearance of severe hypertension, sodium and water retention and congestive failure as complications of hormone therapy is much more frequent in the presence of renal involvement. Occasional exceptions to this have been reported.[13, 14] If the renal involvement is not pronounced, albuminuria and hematuria may actually subside. Little is known about the influence of the hormones on the lupus angiitis. Harvey and co-workers[14] have reported disappearance of Raynaud's phenomena under the treatment with the hormones. The cardiac manifestations, pericarditis and myocarditis, may improve to a certain extent if good renal function is present. Such improvement is evidenced by the disappearance of congestive failure and decrease in heart size. At times disappearance of cardiac murmurs has been observed. However, certain

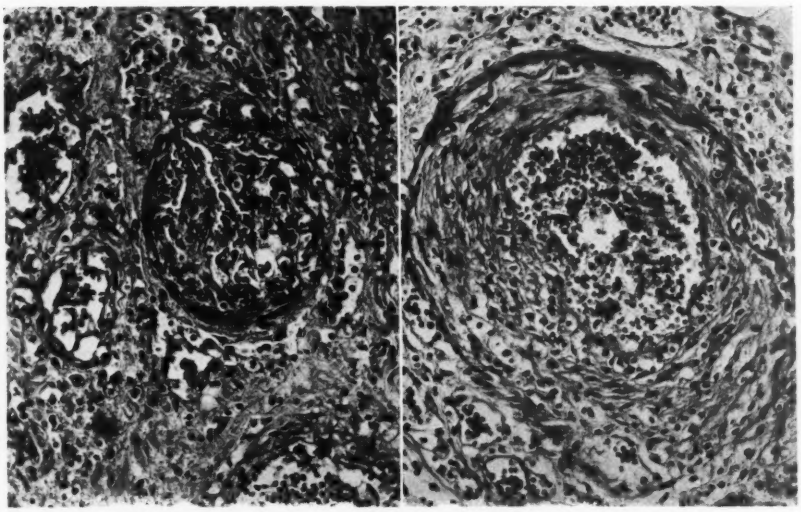


FIG. 6. *Endarteritis Occurring during Cortisone Therapy.* This 61 year-old white man, with typical severe rheumatoid arthritis of fifteen years duration, had received 100 mg. cortisone daily for about four years, then the dose was reduced to 37.5 mg. Soon thereafter cyanosis of several finger tips developed, followed by gangrene. A muscle biopsy revealed foci of arteritis and necrotizing myositis. The dose of cortisone was increased to 300 mg. daily but the patient pursued a progressive downhill course and died in shock about one month later.

The autopsy revealed extensive lesions in the intima of the arterioles, ranging from edema with swelling of endothelial cells to a marked proliferating endarteritis. Nearly all the organs were involved. In the small and large intestines, these lesions led to the formation of multiple ulcers with perforation. The patient also had coronary arteriosclerosis with a recent myocardial infarct. The adrenal glands were atrophic.

Figure 6*A* shows an early lesion in an arteriole of the intima with irregular arrangement of endothelial cells. Figure 6*B* illustrates an arteriole of the submucosa of the small intestine showing a later stage with proliferation and fibrous thickening. (× 200, hematoxyline-eosine stain).

patients thought to have normal cardiac function have developed congestive failure while under hormonal therapy and at necropsy lupus myocarditis was demonstrated. There is a paucity of reports on autopsied cases of systemic lupus erythematosus treated with the hormones. Histologic evidence of healing of the lesions has not been reported.

Necrotizing angiitis may also be benefitted by corticotropin and corticosteroid treatment. Schick and Kvale[53] have recently reviewed their own observations and the pertinent literature on the subject and have demonstrated that symptomatic improvement occurs under therapy. Here, actual histologic evidence of healing of the lesions to a greater extent than would be expected in the untreated case was reported. The healing is associated, however, with fibrosis which may lead to occlusion of the vessels and infarction of the dependent tissues. Deaths could be attributed to such occlusion in the coronary and renal vessels. Hence it would appear that treatment to be effective must be initiated early in the course of the disease before extensive involvement has occurred.

In one case observed recently at the Michael Reese Hospital, an endarteritis (the patient succumbed) occurred during the treatment of chronic rheumatoid arthritis with cortisone (fig. 6A and B). It is of interest that other observers have described periarteritis occurring under hormone therapy in patients with rheumatoid arthritis of years duration.[54] Furthermore, it has been shown that withdrawal or reduction of cortisone after pro-

longed therapy may be followed by extensive angiitis.[55]

Experimental evidence exists that cortisone has a profound influence upon vascular responses. Actual reduction of blood flow through sites of inflammatory tissue has been demonstrated following the administration of cortisone or ACTH. A permissive action of the steroids upon vasoconstriction by nor-adrenaline was described.[56] Reduction of the number of capillaries in granulation tissue has been repeatedly demonstrated[57] and an alteration of the course of newly formed capillaries in such tissues was described.[58] Aggravation of the first stage of the Schwarzman phenomenon by cortisone was reported.[59] All these observations indicate that the action of corticosteroids upon the vessels is a complex but definite one. Although one form of experimental angiitis may be inhibited by cortisone, it is conceivable that the same steroid may exert an unfavorable effect upon the vasculature under circumstances poorly understood.

The effect of corticosteroid therapy upon cardiovascular manifestations in progressive systemic sclerosis has been questionable. The Raynaud syndrome was not benefitted in any of the cases observed by us. There is little information concerning the effect upon cardiac complications. In our experience there was no improvement. One, at best temporary, response to corticotropin was reported.[60] The influence upon the renal vessels may be unfavorable. In several instances the occurrence of severe hypertension and azotemia has been reported.[61, 62] O'Leary and Erickson[63] have even stated that for this reason steroid therapy is contraindicated in this condition. However, the prognosis of heart failure due to progressive systemic sclerosis is so poor that a trial with steroid therapy seems warranted. The newer steroids which have less salt retaining effect may be of greater value.

In dermatomyositis there may be a favorable effect on the general symptomatology but insufficient information exists concerning the effect upon cardiovascular manifestations.

In serum sickness which, as was stated before, is a self-limited disease, the course may be considerably shortened by steroid therapy. Electrocardiographic evidence of myocardial involvement should be an indication for a prompt initiation of treatment. In one case, observed by us, there seemed to be a rapid disappearance of a grade 3 systolic murmur, which occurred early in the course of a penicillin reaction.

Concluding Remarks

Involvement of the heart and blood vessels in collagen diseases is extensive and represents an integral part of the disease process which affects connective tissue structures as a whole. Striated muscle and the myocardium may participate in the pathological reactions and must therefore be included in the considerations of these disease processes. It is mainly on the basis of the clinical picture that the differentiation of the various syndromes can be made. The pathology shows many overlapping features.

Our knowledge of the etiologic agents and mechanisms causing the various disease entities is inadequate. Attempts to understand biochemical and functional alterations of the tissues involved and to correlate them with the structural changes have been made only quite recently. So far these newer approaches have shown most rewarding results. At least in systemic lupus erythematosus and in some types of polyangiitis, processes have been recognized which go beyond pure morphologic description. In the former, they have led to the recognition of the LE cell phenomenon which, apart from its most important theoretic significance, has permitted the identification of the disease by a laboratory method which is nearly specific. The latter syndrome has been reproduced in experimental animals and is thus open to further investigation of its dynamics.

One of the unsolved problems in this disease group is concerned with the factors which maintain the pathologic process for a number of years and render it self-perpetuating. So far, experimental work has been able to reproduce some of the characteristic features but has not succeeded in inducing their progression, as can be observed clinically. This raises the question of the nature of the mechanisms which operate to maintain the steady state of connective tissue structures under normal condi-

tions and which apparently become insufficient in disease.

Experimental studies have revealed many mechanisms of cardiovascular responses under various pathologic conditions and such studies should be applied more intensively to the elucidation of collagen diseases. It is the early stage which requires intensive investigation before the terminal changes seen at autopsy have occurred. There must be a stage in these diseases preceding morphologic alteration which is expressed in functional and biochemical abnormalities of the tissues involved. The recognition of such early changes would enhance our understanding of the processes which have been discussed above.

Acknowledgment

We wish to acknowledge gratefully the assistance of Dr. A. Rywlin in reviewing the autopsied material and the histologic sections of the cases presented in this paper.

REFERENCES

[1] Rich, A. R. and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. Bull. Johns Hopkins Hosp. **72:** 65, 1943.

[2] Klemperer, P.: Pathology of Systemic Lupus Erythematosus. *In*, Progress in Fundamental Medicine, J. F. A. McMannus, ed. Philadelphia, Lea and Febiger, 1952, p. 51.

[3] Meyer, K.: The Chemistry of the Mesodermal Ground Substances. The Mechanism of Inflammation. Montreal, ACTA, Inc., 1953, p. 170.

[4] Schubert, M.: Chemistry of Connective Tissue. *In*, The Musculoskeletal System, V. M. Ashford, ed. New York, Macmillan, 1952, p. 41.

[5] Dorfman, A.: Metabolism of the mucopolysaccharides of connective tissue. Pharmacol. Rev. **7:** 1, 1955.

[6] Gross, J.: The Structure and Biological Activity of Connective Tissue. The Musculoskeletal System, V. M. Ashford, ed. New York, Macmillan, 1952, p. 1.

[7] Randall, J. T.: Nature and Structure of Collagen. New York, Academic Press, 1953.

[8] Klemperer, P.: The Significance of the Intermediate Substance of the Connective Tissues. The Harvey Lectures, 1953–1954. Charles C Thomas, 1955, p. 100.

[9] Duff, G. L.: Collagen Diseases. *In*, The Musculoskeletal System, P. 243. Macmillan, New York, 1952.

[10] Ehrich, W. E.: Nature of collagen diseases. Am. Heart J. **43:** 121, 1952.

[11] Shearn, M. A. and Pirofsky, B.: Disseminated lupus erythematosus. Arch. Int. Med. **90:** 790, 1952.

[12] Jessar, R. A., Lamont-Havers, W. and Ragan, C.: Natural history of lupus erythematosus disseminatus. Ann. Int. Med. **38:** 717, 1953.

[13] Dubois, E. L.: The effect of the LE cell test on the clinical picture of systemic lupus erythematosus. Ann. Int. Med. **38:** 1265, 1953.

[14] Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L. and Schoenrich, E. H.: Systemic lupus erythematosus: Review of the literature and clinical analysis of 138 cases. Medicine **33:** 291, 1954.

[15] Pirani, C. L., Kark, R. M. and Muehrcke, R. C.: Diseases of the kidney studied by percutaneous kidney biopsy. Proc. Inst. Med., Chicago. **20:** 290, 1955.

[16] Gross, L.: The cardiac lesions in Libman-Sachs disease with a consideration of its relationship to acute diffuse lupus erythematosus. Am. J. Path. **16:** 375, 1940.

[17] Huff, S. E., Taylor, H. L. and Keys, A.: Observations on Peripheral Blood Flow in Chronic Lupus Erythematosus. J. Invest. Dermat. **14:** 21, 1950.

[18] Gilje, O., O'Leary, P. A. and Baldes, E. J.: Capillary microscopic examination in skin diseases. Arch. Dermat. & Syph. **68:** 136, 1953.

[19] Klemperer, P., Pollack, A. D. and Baehr, G.: Pathology of disseminated lupus erythematosus. Arch. Path. **32:** 569, 1941.

[20] Friedberg, C. K. and Gross, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease; with a note on abdominal rheumatism. Arch. Int. Med. **54:** 170, 1934.

[21] Horton, B. T., Magath, T. B. and Brown, G. E.: An undescribed form of arteritis of the temporal vessels. Proc. Staff Meet., Mayo Clin. **7:** 700, 1932.

[22] Zeek, P. M.: Periarteritis Nodosa and Other Forms of Necrotizing Angiitis. New England J. Med. **248:** 764, 1953.

[23] Churg, J. and Strauss, L.: Allergic granulomatosis, allergic angiitis and periarteritis nodosa. Am. J. Path. **27:** 277, 1951.

[24] Mowrey, F. H. and Lundberg, E. A.: The clinical manifestations of essential polyangiitis (periarteritis nodosa), with emphasis on the hepatic manifestations. Ann. Int. Med. **40:** 1145, 1954.

[25] Sinclair, W. and Nitsch, E.: Polyarteritis nodosa of the coronary arteries: Report of a case with rupture of an aneurysm and intrapericardial hemorrhage. Am. Heart J. **38:** 898, 1949.

[26] Askey, J. M.: Spontaneous rupture of a papillary muscle of the heart. Am. J. Med. **9:** 528, 1950.

[27] Harrison, C. V.: Giant cell or temporal arteritis: A review. J. Clin. Path. **1:** 197, 1948.

[28] Morrison, A. N. and Abitbol, M.: Granulomatous arteritis with myocardial infarction. Ann. Int. Med. **42:** 691, 1955.

[28a] Getzowa, S.: Cystic and compact pulmonary sclerosis in progressive scleroderma. Arch. Path. **40:** 99, 1945.

[29] Beerman, H.: Visceral manifestations of scleroderma: Review of recent literature. Am. J. M. Sc. **216:** 458, 1948.

[30] Biegelman, P. M., Goldner, F., Jr. and Bayles, T. B.: Progressive systemic sclerosis (scleroderma). New England J. Med. **249:** 45, 1953.

[31] Leinwand, I., Duryee, A. W. and Richter, M. N.: Scleroderma (based on a study of over 150 cases). Ann. Int. Med. **41:** 1003, 1954.

[32] Moore, H. C. and Sheehan, H. L.: The kidney of scleroderma. Lancet **1:** 68, 1952.

[33] Baldwin, E. deF., Cournand, A. and Richards, D. W., Jr.: Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. Medicine **28:** 201, 1949.

[34] Spain, D. M. and Thomas, A. G.: The pulmonary manifestations of scleroderma—An anatomical physiological correlation. Ann. Int. Med. **32:** 150, 1952.

[35] Weiss, S., Stead, E. A., Jr., Warren, J. V. and Baily, D. T.: Scleroderma heart disease. Arch. Int. Med. **71:** 749, 1943.

[36] Goetz, R. H.: The heart in generalized scleroderma (progressive systemic sclerosis). Angiology **2:** 555, 1951.

[37] Mahrer, P. R., Evans, J. A. and Steinberg, I.: Scleroderma: Relation of pulmonary changes to esophageal disease. Ann. Int. Med. **40:** 92, 1954.

[38] Austrian, R., McClement, J. H., Renzetti, A. D., Jr., Donald, K. W., Riley, R. L. and Cournand, A.: Clinical and physiological features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion. Am. J. Med. **11:** 667, 1951.

[39] Boyd, J. A., Patrick, S. I. and Reeves, R. J.: Roentgen changes observed in generalized scleroderma. Arch. Int. Med. **94:** 248, 1954.

[40] Curtis, A. C., Blaylock, H. C. and Harrell, E. R., Jr.: Malignant lesions associated with dermatomyositis. J.A.M.A. **150:** 844, 1952.

[41] Sheard, C., Jr.: Dermatomyositis. Arch. Int. Med. **88:** 640, 1951.

[42] O'Leary, P. A. and Waisman, M.: Dermatomyositis: Study of 40 cases. Arch. Dermat. & Syph. **41:** 1001, 1940.

[43] Kinney, T. D. and Maher, M. M.: Dermatomyositis: A study of 5 cases. Am. J. Path. **16:** 561, 1940.

[44] Wainger, C. K. and Lever, W. F.: Dermatomyositis. Arch. Dermat. & Syph. **59:** 196, 1949.

[45] Pagel, W., Woolf, A. L. and Asher, R.: Histological observations on dermatomyositis. J. Path. & Bact. **61:** 403, 1949.

[46] Wedgwood, R. J. P., Cook, C. D., and Cohen, J.: Dermatomyositis: Report of 26 cases in children with a discussion of endocrine therapy in 13. Pediatrics **12:** 447, 1953.

[47] Mendeloff, J.: Myocardial changes in dermatomyositis. North Carolina M. J. **15:** 15, 1954.

[48] Clark, E. and Kaplan, B.: Endocardial, arterial and other mesenchymal alterations associated with serum disease in man. Arch. Path. **24:** 458, 1937.

[49] Goldman, M. J. and Lau, F. J. K.: Acute pericarditis associated with serum sickness. New England J. Med. **250:** 278, 1955.

[50] Roussak, N. J.: Myocardial infarction during serum sickness. British Heart J. **16:** 218, 1954.

[51] Contro, S., and Mond, E.: Electrocardiographic changes in serum sickness. In preparation.

[52] Soffer, L. J., Elster, S. K. and Hammerman, D. J.: Treatment of acute disseminated lupus erythematosus with corticotropin and cortisone. Arch. Int. Med. **93:** 503, 1954.

[53] Shick, R. M. and Kvale, W. F.: Periarteritis Nodosa and Temporal Arteritis. *In*, Peripheral Vascular Diseases. E. V. Allen, N. W. Barker, and E. A. Hines, eds. Ed. 2, Philadelphia, Saunders, 1955, p. 344.

[54] Levin, M. H., Revo, B. J., Scott, W., Figueroa, W. G., Fred, L. and Barrett, T. F.: The prolonged treatment of rheumatoid arthritis with cortisone and corticotropin. Am. J. Med. **14:** 265, 1953.

[55] Slocumb, C. H.: Rheumatic complaints during chronic hypercortisonism and syndromes during withdrawal of cortisone in rheumatic patients. Proc. Staff Meet., Mayo Clin. **28:** 655, 1953.

[56] Fritz, I. and Levine, R.: Action of adrenal cortical steroids and nor-epinephrine on vascular responses to stress in adrenalectomized rats. Am. J. Physiol. **165:** 456, 1951.

[57] Taubenhaus, M. and Amromin, G. D.: The effects of the hypophysis, thyroid, sex steroids and the adrenal cortex upon granulation tissue. J. Lab. & Clin. Med. **36:** 7, 1950.

[58] ——, Jacobson, M., Morton, J. V. and Levine, R.: Parallel inhibition of granulation tissue by cortisone, hydrocortisone, dibenamine and banthine. Proc. Soc. Exper. Biol. & Med. **84:** 646, 1953.

[59] Thomas, L. and Good, R. A.: The effect of cortisone on the Schwartzman reaction. J. Exper. Med. **95:** 409, 1952.

[60] Barrett, N. W. and O'Brien, W.: Heart disease in scleroderma. British Heart J. **14:** 421, 1952.

[61] Sharnoff, J. G., Candio, H. L. and Stein, L. D.: Cortisone treated scleroderma: Report of a case with autopsy findings. J.A.M.A. **145:** 1230, 1951.

[62] Lunseth, J. H., Baker, L. A. and Shifrin, A.: Chronic scleroderma with acute exacerbation during corticotropin therapy: Report of a case with autopsy observations. Arch. Int. Med. **88:** 783, 1951.

[63] O'Leary, P. A. and Erickson, J. B.: Use and abuse of cortisone and corticotropin (ACTH) in dermatology. J.A.M.A. **152:** 1695, 1953.

CLINICAL CONFERENCES

EDITOR: EDGAR V. ALLEN, M.D.

Associate Editor: RAYMOND D. PRUITT, M.D.

A Patient with Circulatory Complications Following an Exploratory Celiotomy for Unexplained Jaundice

By JOSEPH E. FLYNN, M.D. AND FREDERICK R. BAILEY, M.D.

AN internist is often called as a consultant for certain postoperative complications. One of these is lower nephron nephrosis; another is hemorrhagic pancreatitis. Both are associated with some degree of shock, but in lower nephron nephrosis the shock usually precedes the renal ischemia, whereas in pancreatitis, the shock usually follows the pancreatic involvement.

In the case to be presented, the patient had both a pancreatitis and a lower nephron nephrosis. The appearance of the two lesions following an exploratory celiotomy accounted for a complex clinical picture. In this instance, the autopsy permitted an accurate reconstruction of the sequence of events.

It should also be mentioned that in this presentation, the discussions by the clinician and the pathologist were originally given at a clinicopathologic conference.*

CLINICAL HISTORY

A 34-year old man was admitted to the hospital April 4, 1953, because of chills, fever and jaundice of three days' duration. His previous health had been excellent. His position as a trade representative necessitated frequent trips to the tropics. On such journeys, episodes of diarrhea were not unusual. These were afebrile and were characterized by the presence of watery stools which did not appear grossly to contain blood or pus. The diarrhea promptly disappeared when he returned to a temperate climate.

Five months before his death, he had been admitted to a hospital for appraisal following an attack of diarrhea. There were no significant abnormalities on physical examination, except for an allergic rhinitis. The urine, blood counts, sedimentation rate, basal metabolic rate, serum nonprotein nitrogen, blood sugar and electrocardiogram were all normal. X-ray films of chest, a barium enema and proctoscopy were negative. Two examinations of the stool for protozoa and ova were negative. Four months prior to his final hospital admission, he went to Trinidad. Again he developed diarrhea. In Trinidad he swam in stream-fed pools, but he did not subsequently develop a rash or itching of the skin. He then went to Rio de Janeiro. His diarrhea disappeared, but while there he had an illness characterized by cough, pain in the chest and a rise of temperature to 104 F. A diagnosis of pneumonia was made. Following treatment with penicillin, he promptly recovered, except for a dry cough which persisted, and a loss of 16 pounds. While still in Rio de Janeiro, three months before his final admission, he received an injection of influenza vaccine. A common syringe and needle were used for the inoculation of several people, but the needle was said to have been flamed between injections. He then went to Argentina where his diarrhea returned. It was characterized by three or four bowel movements a day. Two and one-half months before his last hospitalization he went to Panama. Here he had a sore throat and was given aureomycin. The next six weeks were spent in New York. Self administration of aureomycin was continued. His sense of well being gradually returned; his diarrhea disappeared and he regained all of his lost weight. One month before admission,

From the Department of Pathology, University of Missouri School of Medicine, Columbia, Mo., and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

* American College of Physicians Postgraduate course, Columbia University, College of Physicians and Surgeons, New York City, March 22–26, 1954.

he went to Mexico for 10 days. While there his diarrhea recurred and he had night sweats. Following his return to New York he tired easily and continued to have a mild diarrhea. Four days prior to entry he became extremely weak after chopping down some trees. He had a shaking chill and a rise of temperature to 103 F. Following an injection of penicillin, his temperature returned to normal and remained there. However, anorexia, persistence of diarrhea and the appearance of dark urine led to admission to the hospital.

Physical examination on the day of admission revealed a temperature of 100 F., a pulse of 90 beats per minute, and a blood pressure of 130/90 mm. Hg. He did not appear to be acutely ill. There was slight icterus. Examination of the heart and lungs was negative. The liver edge was tender and could be palpated three-finger breadths below the costal margin. One observer believed he could just palpate the tip of the spleen. There were no other abnormal findings.

Laboratory studies were reported as follows: The urine contained bile and a very faint trace of albumin. A complete blood count was normal save for the presence of nine per cent eosinophiles. The erythrocyte sedimentation rate was normal. The stool contained no blood. Seven specimens of stool were examined for ova and protozoa and four specimens were cultured for enteric pathogens with negative results. Three examinations of the sputa were negative for parasitic ova. No bile was obtained on duodenal drainage, and no crystals were found in the material aspirated. The serum bilirubin was 3.6 mg. per 100 cc. (immediate, direct); the alkaline phosphatase was 2.7 Bodansky units; the non-protein nitrogen was 28 mg. per 100 cc.; the serum protein 7.5 Gm. per 100 cc. (albumin 4.7, globulin 2.8); and the serum cholesterol was 181 mg. per 100 cc. The cephalin-flocculation and thymol-turbidity reactions were negative as were the intracutaneous test for schistosomiasis, the heterophile and brucella agglutinations, and the Widal test. The prothrombin time was 16.3 seconds (control 15).

The patient's course in the hospital was afebrile. Itching of the skin was troublesome, and spider angiomata appeared. The alkaline phosphatase rose to 14 Bodansky units and later fell to 10. The serum bilirubin rose gradually to 16.7 mg. per 100 cc. The serum cholesterol rose to 415 mg. per 100 cc. with 25 per cent esters. There was a 17 per cent decrease in free cholesterol on 24-hour incubation.[1] The cephalin-flocculation test became questionably positive, and the thymol-turbidity reaction was 3 plus.

One month following entry, an exploratory celiotomy was performed. The liver was found to be of normal size. The biliary passages were slightly smaller than normal. The common bile duct and the gall bladder were collapsed and empty. The ampulla of Vater was normal. Exploration of the common bile duct with a probe was difficult because of its small size. The junction of the hepatic ducts appeared to be about 1.5 cm. within the substance of the liver. A probe could not be passed beyond this point. The surgeon thought the inability to pass the probe was probably related to the presence of a neoplasm. The entire operation lasted four hours. A biopsy of the liver and the ampulla of Vater was obtained. The pathologist's report was "obstructive condition of the bile duct system and focal necrosis of the liver; normal ampulla of Vater."

The post-operative course was stormy. There were nausea and vomiting. Oliguria was present for the first three days. The non-protein nitrogen rose to 127 mg. per 100 cc. and continued to rise even after the output of urine had returned to normal. The jaundice increased with the serum bilirubin levels varying from 20 to 30 mg. per 100 cc. He developed an anemia, hyponatremia, and edema. Death occurred three weeks after the operation.

Discussion

Dr. Bailey: In attempting to arrive at a diagnosis I shall try to exclude certain conditions. The possibility of extrahepatic obstruction of the biliary tract is eliminated by the findings at operation. There is no evidence to support the diagnosis of schistosomiasis. Amebiasis is unlikely because of the tendency of the diarrhea to subside promptly on each return from the tropics and the reputedly negative stool examinations for amebas. A pure hepatocellular type of hepatitis seems unlikely in view of the chemical studies of liver function.

I shall accept the illness in Rio de Janeiro as being pneumonia and unrelated to the present illness.

The elevation of the serum bilirubin, alkaline phosphatase and total cholesterol levels points to the presence of obstructive jaundice. The moderate rise in globulin, the positive thymol-turbidity reaction and the moderate drop in the percentage of esterified cholesterol are consistent with derangement of cellular function secondary to prolonged obstruction.

The findings at operation clearly place the obstruction as intrahepatic. Therefore, I believe that the differential diagnosis must lie between cholangiolitic hepatitis and a car-

cinoma at the exact point of junction of the hepatic ducts to form the common bile duct.

What did the surgeon's probe hit? Was it a carcinoma or was it stopped by the small caliber of the biliary ducts?

There is much in the history to suggest that the patient might have had the socalled cholangiolitic type of hepatitis. He had been travelling in the tropics and received an injection with a possibly inadequately sterilized needle. Furthermore, he was an allergic individual (as evidenced by a vasomotor rhinitis) and he had received penicillin on two occasions as well as large amounts of aureomycin. In this connection, Hanger and Gutman[2] have called attention to drug sensitization (arsenicals) as a possible factor in the causation of cholangiolitic hepatitis.

I therefore favor the diagnosis of cholangiolitic hepatitis. While it is impossible to rule out the presence of carcinoma at the junction of the hepatic ducts, the rarity of this lesion puts it distinctly in second place.

Why did he have renal "shut-down" and uremia postoperatively? It must be remembered that the operation lasted four hours, that the common duct was opened and probed and that a careful exploration was carried out. Patients with severe disease of the liver are less likely to tolerate prolonged anesthesia and lengthy surgical procedures. Moreover, they are often susceptible to postoperative shock. I suspect therefore that the renal failure was due to acute tubular necrosis ("lower nephron nephrosis").

My clinical diagnoses are: 1. Cholangiolitic hepatitis. 2. Acute tubular necrosis.

Autopsy

Dr. Flynn: At the time of autopsy, the main anatomic lesions were present in three organs: the liver, the pancreas and the kidneys. The other viscera, including the brain, showed no significant abnormalities.

We shall begin first with the liver. It was grossly normal. There was no intrahepatic biliary obstruction and there was no extrahepatic biliary obstruction. You will recall that the surgeon thought an intrahepatic biliary obstruction might have existed. Actually, the difficulty the surgeon had in probing the duct, was related to the early bifurcation of the somewhat-smaller-than-normal intrahepatic bile ducts. The severe jaundice the patient had was related to a hepatitis; a hepatitis that was obviously present in the original biopsy, but which was not properly diagnosed at that time, because the pathologist was swayed by the belief that the surgeon had found an intrahepatic biliary obstruction.

You will recall that a hepatitis of viral origin is sometimes divided into two types: the hepatocellular, and the cholangitic or cholangiolitic.[3] These two types differ clinically as well as anatomically. The hepatocellular type commonly involves the liver cords, usually in the center of the lobule, whereas the cholangitic type involves the portal canals and occasionally, to some extent, the periportal hepatic tissue. Figure 1 shows the microscopic appearance of the biopsy of the liver. Near the center of the photograph is an area of necrosis. These areas were numerous but fairly small and would not in themselves explain the severe clinical findings of liver damage. However, there was also a cholangitic involvement. Figure 2 shows the low-power appearance of the liver biopsy. It is obvious that the portal canal is edematous and heavily infiltrated by inflammatory cells. The cholangitic lesion helps to explain the severe jaundice because of the reduction in the width of the bile ducts. Although it is not well appreciated, a slight reduction in the width of the biliary tree enormously retards the rate of flow of bile. It will be recalled that the expression for the rate of flow of liquid in a capillary is given by the formula

$$Q = \frac{\pi R^4 P}{8VL}$$

where Q is the rate of flow, R is the radius, P is the pressure, V is the viscosity and L is the length. In this formula the fourth power relationship of the radius is very important. For example, if the lumen of a bile duct had a radius of 1.0 mm., then R^4 is 1.0. If the lumen were reduced in size to a radius of 0.5 mm., then R^4 will be 0.0625. Obviously, as the numerator of this equation becomes smaller, the rate of flow (Q) is reduced.

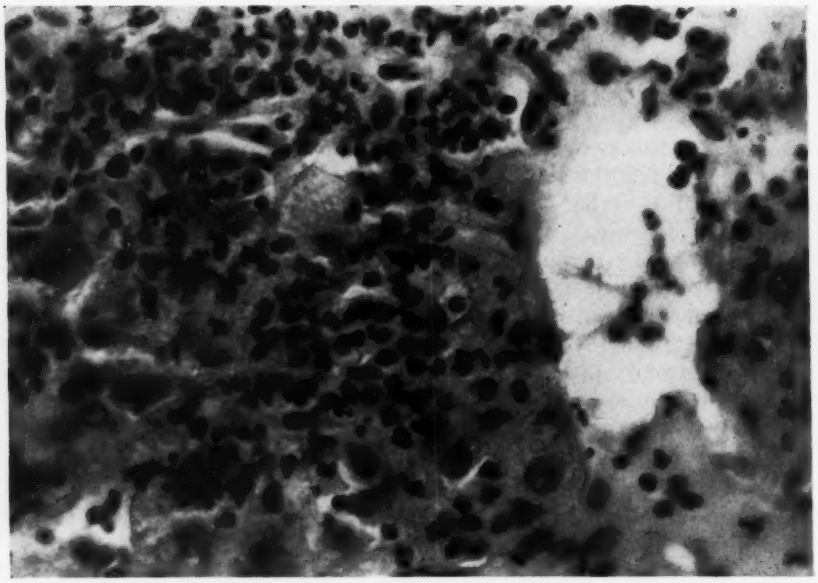


FIG. 1. A section of liver biopsy showing focal necrosis and an inflammatory cell infiltration. These changes are most marked in the center of the field. The space on the right is the lumen of a small hepatic vein.

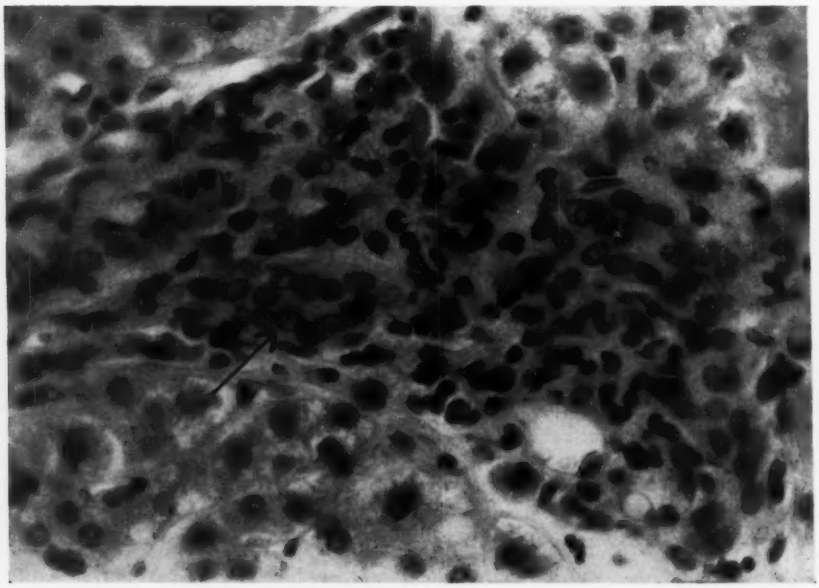


FIG. 2. This section of the liver biopsy includes the portal canal and adjacent parenchyma. The latter is seen at the upper left, upper right and lower left margins. The arrow points to a small compressed bile duct. The cellularity of the portal canal is increased due to the presence of numerous inflammatory cells.

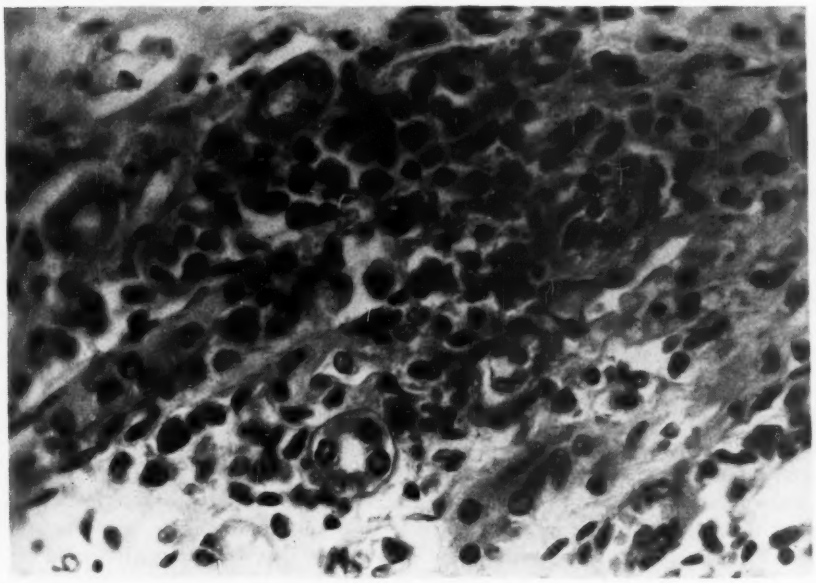


FIG. 3. This is a section of kidney with severe lower nephron nephrosis. The tubular epithelium is markedly necrotic. In addition there is dissolution of the basement membrane of the necrotic tubules and a peritubular inflammatory cell infiltration.

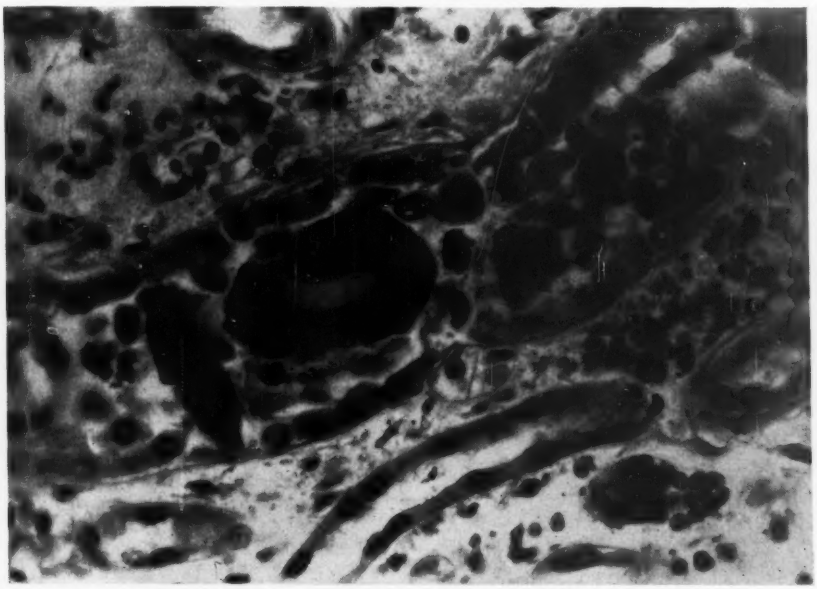


FIG. 4. Passing obliquely across this section of kidney is a distal convoluted tubule. Its lumen contains amorphous fragmented material.

At the time of autopsy, the hepatitis had largely subsided. The patient, however, as you recall, continued to be jaundiced. This was related to another complication: acute hemorrhagic pancreatitis. The incidence of acute hemorrhagic pancreatitis is approximately 0.01 per cent to 0.1 per cent in exploratory celiotomy.[4] When it occurs, the diagnosis is seldom made before death. The pancreatitis was probably due to a variety of factors including trauma to the pancreas, reflux of bile into the pancreatic duct and, possibly, to the jaundice itself. It is known that jaundice predisposes the pancreas to this change, but why it does is not clear. At the time of autopsy, the pancreas was merely a necrotic bag of blood.

In addition to the pancreatitis, there was a severe lower nephron nephrosis. This explains the very severe oliguria and electrolytic changes in the blood that developed terminally. The lower nephron nephrosis was characterized, as it always is, by patchy tubular necrosis, segmental disruption of the basement membrane, and a peritubular inflammatory reaction.[5] Figure 3 shows the microscopic appearance of the kidney. It is obvious that considerable peritubular inflammation is present. Figure 4 indicates that this inflammation is secondary to tubular necrosis. On one side the tubular epithelium is intact and the basement membrane can be identified. On the opposite side the epithelium is necrotic, the basement membrane is segmentally disrupted and the tubular lumen is exposed to the interstitial connective tissue. Within the tubular lumen are desquamated epithelial cells, bile-stained cellular fragments, leukocytes and precipitated material of undetermined origin. At one time the casts were thought to explain the oliguria on the basis of mechanical obstruction. It is now known, as Oliver and his co-workers have pointed out,[5] that this is probably related to decreased glomerular filtration and reduced tubular flow because of a loss of fluid through the necrotic tubular wall. Also, as Oliver and his co-workers pointed out, a lower nephron nephrosis represents an anatomic syndrome that follows renal ischemia. This explains why the lower nephron nephrosis occurs in such a wide variety of conditions, including the transfusion reaction, shock, crush syndrome, and so on. The amount of renal damage following renal ischemia is related in large part to the degree and duration of the ischemia. Characteristically, the necrosis involves the tubules, not the glomeruli. There are at least two reasons for the predilective tendency to involve the tubular epithelium: (1) what blood does reach the kidney supplies the glomerulus first, before it enters the peritubular network to supply the tubule; (2) the tubular epithelium is far more metabolically active than is the glomerulus and is, thus, more sensitive to a reduction of blood flow with the concomitant decrease in local oxygen supply. At any rate, the oxygen consumption of the tubule is considerably higher. It is known, of course, that the renal ischemia may persist long after the condition which produced it has disappeared. This can be demonstrated by catheterization studies. The question remains as to why the ischemia persists. Is it related to compression of the blood vessels by the peritubular edema and inflammatory reaction or is it a more subtle mechanism depending upon some humoral or reflex process?

In summary then, the most likely sequence of events would seem to be, first of all, a viral hepatitis, characterized by hepatocellular and cholangitic components. To rule out a mechanical obstruction, an exploratory celiotomy was done. This was followed by an acute hemorrhagic pancreatitis and a lower nephron nephrosis.

REFERENCES

[1] Turner, K. B., McCormack, J. H., Jr. and Richards, A.: The cholesterol-esterifying enzyme of human serum in liver disease. J. Clin. Invest. **32:** 801, 1953.

[2] Hanger, F. M., Jr. and Gutman, A. B.: Postasphenamine jaundice apparently due to obstruction of intrahepatic biliary tract. J.A.M.A. **115:** 263, 1940.

[3] Watson, C. J. and Hoffbauer, F. W.: Problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver. Ann. Int. Med. **25:** 195, 1946.

[4] Blumensaat, C.: Über Pankreatitis nach Operationen am Gallensystem. Beitr. klin. Chir. **181:** 233, 1950.

[5] Oliver, J., MacDowell, M. and Tracy, A.: The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and ischemuric episode. J. Clin. Invest. **30:** 1307, 1951.

ABSTRACTS

BALLISTOCARDIOGRAPHY

Bozal Urzay, V., Merlen, J. J. and Alonso, L.: Effects of Lung Collapse Therapy Upon the Ballistocardiogram. Arch. mal. coeur. **47:** 1026 (Dec.), 1954.

The authors studied, in 35 cases of pulmonary tuberculosis, the effect of pneumothorax, pneumoperitoneum, phrenicectomy and their combinations upon the ballistocardiogram (electromagnetic method according to Dock).

Unilateral pneumothorax, right or left, only rarely caused alterations of the ballistocardiogram. Following bilateral simultaneous pneumothorax, or the other two procedures employed, the amplitude of the ballistocardiogram became smaller affecting equally all deflections, and failed to vary with respiratory movements. These alterations of ballistic forces can be ascribed to the interposition of air, a diminution of ejection time of the right ventricle, and augmentation of resistance to the output of the right ventricle and alterations in the equilibrium of the output of the two ventricles in the course of the respiratory cycle.

PICK

Singewald, M. L.: Ballistocardiography: Past, Present, Future. Ann. Int. Med. **41:** 1124 (Dec.), 1954.

At the present time, three types of the ballistocardiograph are in common use: (1) the Starr high frequency undamped bed, (2) the low frequency critically damped bed of Nickerson, and (3) the direct body pick-up, proposed and popularized by Dock. Thus far, the ballistocardiogram has made little contribution to knowledge of valvular heart disease or of congenital heart disease, with the exception of coarctation of the aorta, in which a reasonably definite pattern is frequently found. Clinically normal subjects may have abnormal records and patients with coronary disease may have normal ones, and one can only speculate upon the meaning of these data. The only test that we have encountered that impressively differentiates between normals and patients with coronary artery disease is one based on the effect of cigarette smoking. Similar ballistocardiographic deterioration followed the sublingual administration of nicotine. Analyses show that the mechanical systems inherent in the Starr high frequency technic, in the Nickerson low frequency technic, and in the direct body pick-up procedures, are all subject to disadvantages bound to lead to distortion and inaccuracy. All of these methods suffer from the fact that the body-platform contacts create oscillations of the body which do not have cardiovascular meaning. These oscillations occur at frequencies which fall in the midst of the ballistocardiographic range and consequently seriously distort the records in both timing and amplitude. It is hoped these follow-ups will reveal that the coronary artery circulations of normal controls with normal ballistocardiograms remain efficient longer than those of controls with abnormal records. Statistically significant figures to make these hopes facts will not be available until such long-term studies, utilizing the conventional and the newer aperiodic ballistocardiographic technics, are completed. The ideal line of progress should connect definitively the physiologic events in the cardiovascular generator with the component waves of as faithful a force ballistocardiogram as can be recorded. When this ideal is attained, then ballistocardiography will provide not only information upon the clinical cardiovascular efficiency not obtainable by other means but also information which is deeply needed by the clinician to guide him both in his therapy and in his predictions of the outcome of his patient's ills.

WENDKOS

ENDOCRINE EFFECTS ON CIRCULATION

Knight, R. P., Jr., Kornfeld, D. S., Glaser, G. H. and Bondy, P. K.: Effects of Intravenous Hydrocortisone on Electrolytes of Serum and Urine in Man. J. Clin. Endocrinol. **15:** 176 (Feb.), 1955.

Five adult subjects, three of whom were well controlled epileptics, were each given an intravenous infusion of either 50 mg. or 100 mg. of hydrocortisone in 5 per cent glucose and 1 per cent ethyl alcohol over a period of four hours. Two normal adult males served as controls, receiving only 5 per cent glucose and 1 per cent ethyl alcohol infusion during the four hour period. Samples of blood and urine were taken for study just before the infusion was begun, at 2 hours and at 4 hours after the start of the infusion. No further samples were taken after the infusion of hydrocortisone was stopped.

All of the subjects receiving hydrocortisone showed a progressive drop in the eosinophil count over the four hour period. The levels of serum sodium and serum chloride showed inconsistent changes over the four hour period, as did the excretion of these two ions in the urine. However, there was a marked increase in the excretion of potassium in the urine of all the experimental subjects, and four out of five subjects showed an increase in serum potassium level equal to from 0.6 to 1.1 mEq. The controls showed no significant change in serum potassium or potassium excretion. The simultaneous increase in serum potassium level and urinary potassium excretion suggests an effect of hydrocortisone not only on the renal tubules but also on the ionic exchanges which take place across the cell membrane, releasing potassium from body cells faster that the kidney can excrete it. Other investigators have demonstrated that the administration of hydrocortisone for longer periods of time results in a drop in the serum potassium level below normal.

CORTELL

Mozziconacci, P. and Caramanian, M. K. Results of Hormonal Therapy of Bouillad's Disease. Arch. mal. coeur **48:** 3 (Jan.), 1955.

The authors report results of cortisone and corticotropin treatment in 267 cases with acute rheumatic fever, observed over a period of at least one month. Cortisone was used in the majority of the instances while corticotropin was applied in urgent cases by intravenous drip. The indications for the use of hormonal therapy and the dosage are outlined, the incidents accompanying the treatment described and the necessity pointed out to keep such patients under close observation.

Hormone therapy is at present the most active therapeutic procedure in acute rheumatic fever. Its success in certain fulminant types of the disease is unquestionable. In the common variety the use of cortisone seems to diminish the number of complications, in particular the incidence and the evolution of cardiac lesions. The conclusion of the authors is that in every attack of rheumatic fever, even when occurring in a mild and apparently benign form, early employment of hormonal therapy is indicated.

PUCK

HYPERTENSION

Snyder, C. H., Bost, R. B., and Platou, R. V.: Hypertension in Infancy, with Anomalous Renal Artery. Pediatrics **15:** 88 (Jan.), 1955.

A case is reported illustrating the truism that hypertension in infancy is always secondary rather than primary. A male infant of nine months of age was investigated for hypertension of fair degree (240/180 mm. Hg). The report gives (approaches to the problem), the various studies done and the final elucidation, when a renal arteriogram was performed. It was found that the infant had an anomalous arterial supply to the right kidney with a double renal artery and numerous aneurysmal dilatations present within the kidney parenchyma. Right nephrectomy was performed. There was marked ischemia of most of the kidney parenchyma and thrombosis in some of the branches of the renal artery. There was a prompt fall in the blood pressure to normal levels. A two year follow-up shows a youngster with normal growth and development and normal blood pressure.

HARVEY

Moyer, J. H., Mills, L. C., Ford, R. V., and Spurr, C.: The Effect of a Head-Up Tilted Position and Ambulation on Renal Hemodynamics and Water and Electrolyte Excretion in Patients with Hypertension, With and Without Renal Damage. J. Lab. and Clin. Med. **45:** 179 (Feb.), 1955.

Twenty male patients with essential hypertension were studied for the effects of 60-degree head-up passive tilting on renal function. An additional seven patients with essential hypertension were studied for the effects of ambulation. In both groups, glomerular filtration rate (GFR), renal plasma flow (RPF), maximum tubular excretory capacity (TmPAH), blood pressure, and the rates of excretion of water, sodium, and potassium were observed.

Mean blood pressure fell 10 per cent in the tilted position. There were even greater declines in values for glomerular filtration rate, renal plasma flow and renal blood flow, the latter indicating an increase in renal vascular resistance. The reductions in glomerular filtration rate and renal plasma flow were parallel. Maximum tubular function (maximum tubular excretory capacity) was also significantly depressed, indicating a reduction in the number of functioning nephrons. The decrease in glomerular filtration rate:maximum tubular excretory capacity ratio, however, demonstrated that

the decline in the number of nephrons was exceeded by the decrease in filtration rate since the latter was more sensitive to changes in hemodynamics. The rate of water and sodium excretion were depressed more than any other process studied. Potassium excretion was only slightly depressed. The reduction in water and sodium excretion during tilting was out of proportion to the fall in glomerular filtration rate, renal plasma flow or tubular excretory capacity, suggesting that there may be factors other than vasoconstriction in operation, possibly neurogenic effects on tubular resorption of sodium and water.

In contrast to the response in the passively tilted position, ambulation resulted in no change in mean blood pressure. However, glomerular filtration rate, renal plasma flow, and maximum tubular excretory capacity were depressed, indicating renal vasoconstriction, but this was not nearly as marked as in the tilting experiments. The response on electrolyte and water excretion to ambulation was also qualitatively similar to the response to passive tilt, but again was not so marked.

There was no significant difference in the reactivity of the severely damaged kidney as compared to the normal ones, and the changes in this series of hypertensive patients closely resembled those seen in normotensive patients. This suggests that the nephrons that remain functional react in a relatively normal manner.

CORTELL

Rowe, G. G., Huston, J. H., Maxwell, G. M., Crosley, A. P., Jr., and Crumpton, C. W.: Hemodynamic Effects of 1-Hydrazinophthalazine in Patients with Arterial Hypertension. J. Clin. Invest. **34:** 115 (Jan.), 1955.

Seventeen patients with essential hypertension but not in cardiac failure received 1-hydrazinophthalazine through a catheter with the pulmonary artery. Twelve subjects experienced minor discomforts. In these persons there was a decrease in vascular resistance in the systemic circulation (−31 per cent) and in the lung (−28 per cent). There was also a fall in systemic arterial pressure and a rise of 33 per cent in cardiac output. However, the calculated left ventricular pressure work was not increased in spite of the increased cardiac output.

The other five subjects experienced a marked fall in blood pressure, pallor, diaphoresis and apprehension; and oxygen had to be administered by mask. In these subjects there was no change in cardiac output. Probably the marked hypotensive effect was due to failure of venous return because of peripheral and splanchnic pooling of blood. This group showed a fall in left ventricular work. Hyperventilation was noted in 14 of the 17 patients.

WAIFE

Kramer, L. B., Horne, R. V., Bellet, S. and Koelle, G. B., The Effect of Intravenous Infusions of the Optical Isomers of Dibozane (McN-181; 1,4-Bis[1,4-Benzodioxan-2-Ylmethyl] Piperazine), an Adrenergic Blocking Agent, Upon Hypertensive Subjects. Am. J. M. Sc. **228:** 614 (Dec.), 1954.

The hypotensive activities and side effects of 3 isomers of Dibozane were examined by means of intravenous infusions of the drugs to a total of 10 hypertensive patients. Observations were made on the blood pressure, pulse rate, electrocardiogram and individual reactions during the infusion. The dextro isomer (80 to 100 mg. in 22 to 45 minutes) produced no significant hypotensive or side effects. The levo isomer (42 to 100 mg. in 17 to 56 minutes) produced significant hypotensive effects in 5 of 10 patients. The side effects observed with this compound included cardiac arrhythmias such as premature contractions of nodal and auricular origins, sinus tachycardia and wandering pacemaker. Other effects included drowsiness, nausea and vomiting, restlessness, and urinary or defecatory urgency. The meso isomer (65 to 100 mg. in 17 to 54 minutes) produced a hypotensive effect in 3 of 10 patients. In addition to the above side effects, certain patients experienced impairment of thinking and recall, and disorientation. The levo isomer was the most potent vasodepresser agent but its therapeutic usefulness is limited by the side effects which may accompany its use.

SHUMAN

Freis, E. D.: Mental Depression in Hypertensive Patients Treated for Long Periods with Large Doses of Reserpine. New England J. Med. **251:** 1006 (Dec. 16), 1954.

Five cases of mental depression in hypertensive individuals are reported. Each patient had received reserpine in doses of 1.0 to 2.0 mg. daily, with the exception of one, who received a dose of 0.25 mg. per day. Some patients also received veratrum alkaloids and others received pentolinium bitartrate with or without 1-hydrazinophthalazine, but Reserpine was the only drug given to all of the patients. The depression cleared in all but one of the patients soon after the reserpine was discontinued. All patients exhibited withdrawal, lethargy and unhappiness. There was no anorexia or weight loss. Two of the patients contemplated suicide. Lesser manifestations of depression observed in other patients have included lack of ambition, crying spells, introspection and lethargy. In every case of the series reported, the reserpine had been given for two months or longer before symptoms of depression appeared. Once the depression developed, simple reduction of dosage failed to relieve the symptoms and it became necessary to stop the drug completely. The author suggests that maintenance doses of reserpine be kept as low as possible, preferably be-

low 0.25 mg. daily, to reduce the likelihood of the development of this syndrome.

ROSENBAUM

PATHOLOGIC PHYSIOLOGY

Coelho, E., Borges, S. Pádua, F., Nunes, A., Barata, M. I., Maltez, J., Pereira, A. and Duarte, C. A.: Relations between the Shape of the P.V.C. Pressure Pulse and the Physiopathology of the Mitral Valve. Cardiologia **26:** 1 (Fasc. 1), 1955.

In order to establish whether mitral regurgitation is typically reflected in the contour of the pulmonary arterial wedge pressure curve, the authors reviewed their material consisting of 30 curves obtained in catheterized patients with a normal mitral valve (hypertension, pericarditis and patent ductus arteriosus) and 180 curves in cases with mitral disease, comprising instances with pure mitral stenosis as well as cases of mitral stenosis associated with moderate or severe grades of regurgitation. Forty-five cases of the mitral group were submitted to commissurotomy.

In some cases with predominant mitral insufficiency a high "systolic" pressure peak was recorded in the P.V.C. curve. However, in other cases with the same degree of regurgitation the "systolic" pressure wave was equal or lower than the presystolic wave. On the other hand, in cases with pure mitral stenosis (two confirmed at surgery), the "systolic" wave was early and higher than the presystolic wave. In 12 cases with mitral regurgitation verified surgically, the P.V.C. pulse presented a normal contour with one exception in which the amplitude of the v wave was marked. These observations led the authors to the conclusion that the contour of the pulmonary arterial wedge pressure curve provides no information concerning the presence or absence of mitral insufficiency.

PICK

Hort, W.: Morphologic Investigations of the Heart Before, during and after Postnatal Adaptation of the Circulation. Virchow Arch. f. path. Anat. **326:** 458 (Fasc. 4), 1955.

The author studied 130 hearts of prematures, newborns and infants by anatomical, histologic and planimetric methods. On the basis of this study and a comparative study in 142 hearts of cats he arrived at the following conclusions. In the last months of pregnancy the musculature of the right ventricle grows more than that of the left ventricle so that in babies born at term the right ventricle weighs more than the left. In the subsequent weeks, however, this difference decreases, first rapidly then slowly. Since this is due to reduction of the weight of the heart and of the size of myocardial fibers of the right ventricles, it represents a physiologic postnatal atrophy of this chamber. In the premature this could be demonstrated at the end of the first week of life. The growth of the left ventricle is rapid and out of proportion to the increase of body weight. Abnormal left ventricular hypertrophy develops in the infant much faster than in the adult.

These anatomic findings suggest the following physiologic processes in the neonatal period. In the last month of pregnancy the output of the right ventricle increases more than that of the left due to augmentation of blood flow through the embryonic lungs. Reduction of pressure in the pulmonary circulation starts soon after birth, probably in the first stage of life. Histologic studies of the closed ductus arteriosus in the cat suggests that the pressure gradient between systemic and pulmonary circulation, developing soon after birth, does not prevent the spontaneous closure of the ductus.

PICK

Overbeck, W., Krock, H. and Biörk, G.: The Evaluation of "Pulmonary Capillary Pressure Curves" in Mitral Lesions. Ztschr. f. Kreislaufforsch. **44:** 22 (Jan.), 1955.

The authors reviewed their material of pulmonary arterial wedge pressure curves obtained in 55 cases of pure mitral stenosis (35 proven at surgery) and 24 cases with mitral insufficiency (10 proven at surgery), the purpose being to determine the validity of the method in differentiating the two conditions.

The characteristic alteration of the wedge pressure curve in mitral stenosis is augmentation of its presystolic portion; it was found only in about half of the respective cases and was absent in auricular fibrillation. The tent-like deflection, considered characteristic of mitral regurgitation was absent in about half of the proven cases and found in several instances in whom stenosis without significant insufficiency was encountered at surgery. It is concluded that the pulmonary wedge pressure curve is of limited value in the differential diagnosis of mitral stenosis and insufficiency, and this only as long as sinus rhythm is present. Noncharacteristic alterations of presystolic and systolic portions of the curves, which were found in about half of the cases, do not permit the exclusion of one or the other condition.

PICK

Telkkä, A. and Mustakallio, K. K.: Proximal or Distal Mercurial Inhibition of Succinic Dehydrogenase in the Kidney Tubule of Rat. Science **121:** 146 (Jan. 28), 1955.

Mercurophylline caused an almost complete inhibition of succinic dehydrogenase in the thick portions of Henle's loops. Activity of the proximal convoluted tubule was reduced, while activity was only slightly reduced in the distal tubule.

Mercuhydrin in the same doses produced a very marked inhibition of succinic dehydrogenase in the proximal tubule, whereas the distal tubule and the thick portion of Henle's loops were scarcely affected.

The amounts of mercury and theophylline were the same for both diuretics. It would seem, therefore, that the different organic components of these drugs are responsible for the differences in enzymatic inhibition.

WAIFE

Schoolman, H. M., Dubin, A. and Hoffman, W. S.: Clinical Syndromes Associated with Hypernatremia. Arch. Int. Med. **95:** 15 (Jan.), 1955.

Over 100 cases of acute hypernatremia seen over a period of four years are discussed. With few exceptions these cases all seem to fall into three categories, which the authors have designated as primary desiccation, central nervous system injury, and diabetic coma after saline therapy. Hypernatremia may result if patients in diabetic coma are treated solely with insulin and saline solutions. The treatment of hypernatremia is the intravenous or oral administration of non-saline fluids. Such treatment is usually successful except in cases of central nervous system injury severe enough to produce death.

BERNSTEIN

Fazekas, J. F., Kleh, J. and Parrish, A. E.: The Influence of Shock on Cerebral Hemodynamics and Metabolism. Am. J. M. Sc. **229:** 41 (Jan.), 1955.

The subjects of this study were found to be in peripheral circulatory failure due to a variety of conditions. Cerebral blood flow, oxygen consumption, vascular resistance and direct arterial blood pressures were determined in each prior to the administration of vasopressor drugs. The mean arterial pressure in the 11 patients was 51 mm. of Hg with a range of 20 to 76 mm. The mean value for cerebral blood flow was reduced to 31.5 cc. per 100 Gm. of brain per minute. There was no apparent correlation between the rate of blood flow and the state of consciousness. The mean value for cerebral metabolic rate was 1.9 cc. and varied from normal to markedly reduced levels. Oxygen extraction, in some cases, was markedly increased; in others, it was reduced. It appears that there are compensatory mechanisms which maintain cerebral metabolism despite a reduction of arterial pressure and cerebral blood flow. In some instances, a decrease in metabolism and oxygen extraction was observed which may result from a failure of the compensatory mechanisms. It is concluded that alterations in cerebral hemodynamics play an important role in the prognosis of shock.

SHUMAN

Yu, P. N., Lovejoy, F. W. Jr., Joos, H. A., Nye, R. E. Jr., Beatty, D. C. and Simpson, J. H.: Studies of Pulmonary Hypertension. VI. Am. Heart J. **49:** 31 (Jan.), 1955.

Studies of pulmonary "capillary" pressure or pulmonary artery wedge pressure and pulmonary artery–pulmonary "capillary" pressure gradient are reported in 150 patients with cardiopulmonary disease, including the effects of acute stress in certain patients. Sixteen of 28 patients with chronic pulmonary disease, five patients with congenital heart disease, and three cases of primary pulmonary hypertension had precapillary pulmonary hypertension and an elevated PAm-PCm gradient. Postcapillary pulmonary hypertension occurred in forty-one of 45 cases of predominant mitral stenosis with elevation of the APm-PCm gradient in two-thirds and with correlation, in general, between the magnitude of the PCm and the PAm-PCm gradient. Postcapillary pulmonary hypertension was observed in 7 of 8 patients after mitral valvuloplasty and in various other examples of impaired left heart flow.

Most cases of congenital heart disease, tricuspid and aortic valve disease, hypertension without failure, and twelve of 28 patients with chronic pulmonary disease had a normal PAm and PCm. Maximal cough caused a sharp rise in PAm and PCm, the latter more marked with chronic pulmonary disease and mitral stenosis. The Valsalva maneuver usually caused a rise in PAm greater than that of PCm. Exercise caused a rise in PAm and little change in PCm in patients with precapillary pulmonary hypertension. In the postcapillary type both PAm and PCm rose significantly with exercise. Acute hypoxia elevated the PAm in unoperated patients with mitral stenosis and elevated the PCm in two of three patients. With chronic pulmonary disease hypoxia elevated the PAm without effect on the PCm.

RINZLER

Jacob, S., Weizel, H., Gordon, E., Korman, H., Schweinburg, F., Frank, H. and Fine, J.: Bacterial Action in Development of Irreversibility to Transfusion in Hemorrhagic Shock in the Dog. Am. J. Physiol., **179:** 523, (Dec.), 1954.

It has been shown that effective antibiotic therapy prolongs the life of dogs subjected to prolonged hemorrhagic hypotension. To be effective, administration of these agents must precede by a few hours the onset of shock. If the stage is reached where transfusion does not restore the circulation, then antibiotics no longer confer protection. Antibiotics may be given either by mouth or by vein and still be effective. This suggests that the bacteria which produced irreversibility to transfusion are to be found in tissues. Although bacteria from the lumen of intestine may invade during shock, they are a dispensable factor. Clostridia are found in dog tissues

during life although the blood is usually sterile. Immediately after death, clostridia are found in blood and tissues. In many cases intestinal aerobes are also present. The last mentioned probably invade in the normal dog too, but are rapidly cleared from the blood. It seems that aerobes are easily destroyed while clostridia are not. Correlation between any specific type of bacteremia and any one antibiotic was not very close.

OPPENHEIMER

Vetter, H., Falkner, R. and Neumayr, A.: The Disappearance Rate of Colloidal Radiogold from the Circulation and its Application to the Estimation of Liver Blood Flow in Normal and Cirrhotic Subjects. J. Clin. Invest. **33:** 1594 (Dec.), 1954.

Colloidal radioactive gold, Au^{198}, in doses of 50 to 100 cc. was injected intravenously into 25 normal controls and 12 patients with hepatic cirrhosis without edema. From the disappearance rate it has been possible to calculate the minimal fraction of the total blood volume perfusing the liver per minute.

By this method the average minimal hepatic blood flow in the controls was 1425 ml. per minute in men and 1010 ml. per minute in women. These values correspond satisfactorily with the results obtained by other methods. In cirrhosis, the disappearance rate was greatly diminished. There is evidence that the disappearance rate is to a large extent related to the hepatic circulation. Calculations of liver blood flow by this method show a reduction from 19 ml. per Kg. in normals to 8 ml. per Kg. in cirrhotics.

WAIFE

Herbst, M. and Gruner, G.: Dynamics of the Right Atrium and the Ostia of the Venae Cavae and their Significance. Arch. f. Kreislaufforsch. **21:** 329 (Dec.), 1954.

The authors studied in a material of 90 angiocardiographies the function of the right atrium—venae cavae system under normal and pathologic conditions. The technic consisted in roentgenkinematographic recordings of intravenous injection of 1 to 2 cc. per Kg. of 70 to 80 per cent contrast material, with 18 to 24 pictures taken per second.

Reflux into the superior vena cava was seen in normals. It represents a normal mechanism of pressure adaptation and has no pathologic significance. Reflux into the system of the inferior vena cava, on the other hand, both systolic and diastolic, occurs only under pathologic conditions with right ventricular overload, in particular in septal defects, and in outflow obstructions, most frequently in Fallot's tetralogy. On the basis of the material examined it was concluded that it indicates the presence of right heart failure. Additional signs of right heart failure manifested in angiocardiograms were irregularities in the contour of the atrial shadow occurring during atrial systole and signs of insufficiency of mechanisms causing closure of the ostium of the superior vena cava.

PICK

Kowalski, H. J., Abelmann, W. H., McNeely, W. F., Frank, N. R. and Ellis, L. B.: The Cardiac Output of Normal Subjects Determined by the Dye-Injection Method at Rest and during Exercise. Am. J. M. Sc. **228:** 622 (Dec.), 1954.

The dye-injection method of Hamilton, using Evans blue dye (0.5 per cent solution) for the determination of cardiac output, was employed in 24 normal subjects at rest, in nine of these during exercise. A bicycle ergometer pedalled at 50 rotations per minute was employed for exercise in recumbency. Free arterial flow was used to secure blood samples. The dye-injection method of estimating cardiac output yielded reproducible results in the subjects studied at rest. Using the results reported by others, there was found to be a small but significant difference between the results obtained by this method and those of the Fick method. The dye-injection technic gives slightly higher values. During exercise the cardiac output results with the dye method show some variation due to the wide spectrum of hemodynamic responses displayed. It is concluded that the injection method of estimating cardiac output can be used at exercise as well as during rest.

SHUMAN

Lasser, R. P., and Loewe, L.: Cardiac and Pulmonary Artery Pressure Pulses in Experimental Mitral Stenosis. Am. Heart J. **48:** 801 (Dec.), 1954.

The response of pulmonary artery systolic and diastolic pressure to acute elevation of left atrial mean pressure was explored in animals with an open chest. The elevation of pressure within the left atrium had been effected by the production of simulated mitral stenosis. Observations were made only in the presence of a well-maintained systemic pressure level and in the absence of observable myocardial ischemia. Under these conditions, pulmonary hypertension was uniformly observed throughout all levels of elevation of left atrial pressure. Elevation of left atrial pressure from 5 mm. Hg to 10 mm. Hg causes a rise in pulmonary artery systolic pressure of an average of 0.6 mm. Hg for each 1 mm. Hg rise in the left atrium and a 0.68 mm. Hg rise in diastolic pressure. Elevation of left atrial pressure from 10 to 20 mm. Hg results in a rise of pulmonary artery systolic pressure by an average of 0.65 mm. Hg for each millimeter of left atrial pressure; for the diastolic pressure, there is a rise of 0.77 mm. Hg under similar conditions. Further elevations in left atrial pressure cause a

widened pulse pressure mainly due to rises in pulmonary systolic arterial pressure.

RINZLER

Millican, R. C.: Tourniquet Shock in Mice. Na^{22} and S^{35}-Plasma Turnover in the Accumulated Fluid in Area of Injury. Am. J. Physiol., **179:** 529 (Dec.), 1954.

Tourniquet trauma produced an area of injury with fluid accumulation. By means of tracer doses of Na^{22} Cl and S^{35} plasma, the turnover of these substances in the fluid was studied. Radio-sodium equilibrated in one to two hours. Entrance of labeled protein into this fluid was much slower. There was 30 per cent equilibration in 2 hours, 55 per cent in 6 hours and 80 per cent in 15 hours. Fluid accumulated in the injured area behaves as a stagnant pool, when exchange of protein is used as a criterion.

OPPENHEIMER

Demunbrun, T. W., Keller, A. D., Levkoff, A. H. and Purser, R. M., Jr.: Pitocin Restoration of Renal Hemodynamics to Pre-Neurohypophysectomy Levels. Effect of Administering Neurohypophysial Extraction Products upon the Reduced Renal Functions Associated with Neurohypophysectomy. Am. J. Physiol., **179:** 429 (Dec.), 1954.

Removal of the neurohypophysis was performed without producing any adenohypophysial dysfunction. Under these experimental conditions, glomerular filtration rate, renal plasma flow and tubular maxima are markedly reduced. Either Pituitrin or Pitocin reversed these observations but Pitressin was ineffective. The authors suggest that these results may constitute replacement therapy with the oxytocic fraction Pitocin. If this is true, it would provide an explanation for the presence of oxytocic principle in the male.

OPPENHEIMER

Gilmore, H. R., and Kopelman, H.: Cheyne-Stokes Respiration. An Oximeter Study. Brit. M. J. 2: 1439, (Dec. 18), 1954.

As indicated by dye time-concentration curves, delay in circulation time results in highest arterial oxygen saturation during the period of apnea. The time course of the curve of arterial oxygen saturation makes it unlikely that fall in oxygen saturation is responsible for end of the period of apnea.

In one patient with chronic Cheyne-Stokes respiration, a lesion of the middle pons was subsequently discovered. In a second patient, diagnosed as having pseudobulbar palsy, embolic lesions from mitral stenosis with atrial fibrillation were thought to have involved corticobulbar pathways. The respiratory center has inspiratory and expiratory components in the medulla. A pneumotaxic center in the pons regulates the respiratory center and is itself regulated by higher centers in the brain. The authors believe that lesions of centers above the medulla altered the sensitivity of the medullary center so that a greater carbon dioxide tension was required for its stimulation. Delay in mean circulation time due to heart disease is probably a significant contributory factor.

Respirations became normal with the administration of oxygen. Carbon dioxide and aminophylline likewise abolished Cheyne-Stokes respiration without affecting peak arterial oxygen saturation.

One patient showed cyclic changes in consciousness with unconsciousness, relative constriction of the pupil, some drop in blood pressure and fall in mean circulation time coinciding with the apneic phase. Since oxygen saturation was highest during the period of apnea, anoxemia per se could not be held responsible for the changes in level of consciousness. Although they had no data bearing directly on this point, they suggest that the facts that carbon dioxide tension is lowest during the apneic phase (Harrison) and that cerebral blood flow is directly related to carbon dioxide tension (Kety and Schmidt) may account for the observations recorded.

MCKUSICK

Edwards, W. S., Siegel, A., and Bing, R. J.: Studies on Myocardial Metabolism. III. Coronary Blood Flow, Myocardial Oxygen Consumption and Carbohydrate Metabolism in Experimental Hemorrhagic Shock. J. Clin. Invest. **33:** 1646 (Dec.), 1954.

From the data detailed in this report, it appears that moderate ischemia, a result of diminished coronary blood flow, can induce specific metabolic changes in heart muscle. A metabolic break may occur between pyruvate and acetate in the glycogenolytic cycle, which may be explained by inhibition of cocarboxylase.

WAIFE

Paldino, R. L., and Hyman, C.: Mechanism Whereby Renin Increases the Rate of T-1824 Disappearance From the Circulation of Rabbits. Am. J. Physiol. **179:** 599 (Dec.), 1954.

It is concluded from these experiments that renin infusion increases capillary permeability for labeled protein. There was also a rather small effect on the reticulo-endothelial system. Angiotonin formed during the infusion is responsible for changes in the dye disappearance curve (rate).

OPPENHEIMER

Schweinburg, E. B., Frank, H. A., and Fine, J.: Bacterial Factor in Experimental Hemorrhagic Shock. Evidence for Development of a Bacterial Factor which Accounts for Irreversibility to

Transfusion and for the Loss of the Normal Capacity to Destroy Bacteria. Am. J. Physiol., **179:** 532 (Dec.), 1954.

Livers from dogs in irreversible hemorrhagic shock contain a lethal factor which is absent from livers of normal dogs. This factor depends on bacterial action during the state of shock. After a two hour bout of hemorrhagic hypotension most dogs recover when transfused. However, such dogs will not recover if they receive an intraperitoneal injection of mashed liver from a dog in terminal hemorrhagic shock although similar mashes from normal dogs also permit recovery as in normal controls. The bacterial factor is also fatal to the donor from which it was obtained at a period longer than two hours. This donor will recover subsequent to transfusion if previously treated with appropriate antibiotics. Bacterial activity and irreversible hemorrhagic shock are closely related. Most normal dogs do not succumb to the bacterial factor. Dogs in hemorrhagic shock succumb because they have lost the ability to inhibit bacterial activity within two hours after shock begins.

OPPENHEIMER

Hyman, C. and Paldino, R. L.: Influence of Reticulo-Endothelial Blockade and Stimulation on the Rate of Disappearance of Evans Blue from the Circulation. Am. J. Physiol. **179:** 594 (Dec.), 1954.

Reticulo-endothelial activity was depressed by thorotrast, antihistamine and evisceration. Under these circumstances the dye disappearance rate was decreased. Histamine increased rate of dye disappearance. This was explained in part by stimulation of reticulo-endothelial system. Nephrectomy increased dye disappearance rate, probably without the reticulo-endothelial system being changed.

OPPENHEIMER

Page, I. H., Del Greco, F. and Corcoran, A. C.: Effects of Pentobarbital Anesthesia, High Spinal Cord Section and Large Doses of Ganglioplegic Agents on Hemodynamic Functions Measured by Dye Dilution. Am. J. Physiol. **179:** 601 (Dec.), 1954.

Vasomotor tone is increased in dogs by pentobarbital. When large doses of ganglioplegic agents are given slowly to sick animals, arterial blood pressure tends to be maintained at or near control values. There is little change in cardiac output or peripheral resistance under these circumstances. The pharmacologic ganglion blockade is considered to be incomplete when these results are compared with spinal transection at C-6. Central blood volume is increased and circulation time prolonged by ganglionic blockade in supine anesthetized dogs. These effects are also different from those in dogs with prior spinal cord section. The authors point out the possible relation to pulmonary disease observed with hexamethonium therapy since ganglion blocking agents increased central blood volumes.

OPPENHEIMER

Beaconsfield, P.: A. Effect of Exercise on Muscle Blood Flow in Normal and Sympathectomized Limbs. B. Collateral Circulation before and after Sympathectomy. Ann. Surg. **140:** 786 (Dec.), 1954.

Using the plethysmographic method, the author studied the effects of periods of arterial occlusion and exercise before and after lumbar sympathectomy in a series of patients with occlusive arterial vascular disorders of the lower extremities. He found that the reactive hyperemia produced by arterial occlusion was unaltered by sympathectomy in limbs with no major arterial obstruction or in limbs which were the seat of common iliac or popliteal arterial obstruction. In patients with femoral artery occlusion or obstruction below the division of the popliteal artery, sympathectomy was associated with a greater increase in blood flow during reactive hyperemia. The time for the return of blood flow to normal after reactive hyperemia was decreased in all patients with arterial block.

The time elapsing after exercise for the calf blood flow to reach its peak was decreased after sympathectomy. In the case of long-standing arterial obstruction, the postexercise hyperemia was maximal immediately after sympathectomy and declined slowly until the fourth postsympathectomy month, after which it became stationary. No increase in collateral circulation was noted in this type of case. On the other hand, sympathectomy performed early in the course of an occlusive arterial disease appeared to accelerate the development of the collateral vessels.

ABRAMSON

Herbst, M.: Experimental Investigations Concerning the Pressure in the Right Heart During Rapid Injection of Fluids Into the Inferior Vena Cava. Arch. f. Kreislaufforsch. **21:** 323 (Dec.), 1954.

The authors studied experimentally the effect of rapid high pressure intravenous injection as used in angiocardiography, upon the pressure in the superior vena cava, the right atrium and right ventricle. In 12 dogs a catheter was introduced through a vein of one forelimb and an amount of 1.2–2.0 cc. per Kg. of physiologic salt solution, or contrast material, was injected through a vein of the other forelimb. The injection of the two materials caused irregularities of the heart and reduction of systemic pressures ascribed by the authors to chemical stimuli, but never a pressure elevation in the venous circulation. In none of the experiments was reflux to the inferior vena cava noted. It would appear that local pressure

alterations caused by the injection are completely balanced proximal to the point of the injection by the elasticity of the venous system.

PICK

PATHOLOGY

McAllen, P. M.: Myocardial Changes Occurring in Potassium Deficiency. Brit. Heart J. **17:** 5 (Jan.), 1955.

The author reports two cases, one with idiopathic steatorrhea and another with ulcerative colitis. Both had clinical and electrocardiographic evidence of prolonged potassium deficiency, widespread myocardial fibrosis with normal coronary arteries. The myocardial fibrosis is attributed to the potassium lack.

SOLOFF

Serbin, R. A. and Chojnacki, B.: Idiopathic Cardiac Hypertrophy. Report of Three Cases, New England J. Med. **252:** 10 (Jan. 6), 1955.

Three cases of idiopathic cardiac hypertrophy, occurring in men aged 28, 38 and 43 years, are reported. These cases are said to bring the total number recorded in the literature to 49. The authors feel that these cases do not fit the criteria of beriberi heart disease. The weights of the hearts in the cases reported ranged from 600 to 800 Gm. Mural thrombi were present in the ventricular chambers in two of the patients. Congestive cardiac failure occurred in all cases. The authors review the various hypotheses which have been developed regarding the etiology of myocardial hypertrophy and the differential diagnosis to be considered in cases similar to those reported. It is suggested that the diagnosis of idiopathic cardiac hypertrophy should be considered when congestive heart failure and cardiac enlargement occur in the absence of angina pectoris, the electrocardiographic pattern of infarction or other demonstrable cause of failure.

ROSENBAUM

Panke, W. and Rottino, A.: Endocardial Fibroelastosis Occurring in the Adult. Am. Heart J. **49:** 89 (Jan.), 1955.

A case of endocardial fibroelastosis occurring in a 24-year-old white female is presented with the prime purpose of suggesting that this endocardial lesion, which is commonly seen in infancy, may indeed persist into adulthood. The cause for the pathologic changes was attributed to involvement of the Thesbesian circulations. Anatomic evidence for this was observed in the narrowed mouths of the Thesbesian vessels and of their lumina along their course in the myocardium.

RINZLER

Perloff, J. K.: Some Unusual Cutaneous, Cardiac and Gastrointestinal Manifestations of Systematized Amyloidosis Associated with Multiple Myeloma. J. Mt. Sinai Hosp. **21:** 195 (Nov.–Dec.), 1954.

The author reports the clinical and autopsy findings of two cases of multiple myeloma in middle aged women, 54 and 48 years old, in whom unusual cutaneous, cardiac and gastrointestinal manifestations of systematized amyloidosis were present. Bence-Jones proteinuria and bone marrow infiltration with myeloma cells were present in both cases. The older patient had generalized bone pain about two years before admission, followed within a year by the onset of angina pectoris and congestive heart failure, which was moderately progressive until death. In addition she developed virtually total alopecia and a patchy macular and papular erythematous skin eruption. Weight loss, anorexia, nausea and vomiting were prominent symptoms. The second patient presented with progressive bone pain about one year before death, with gradually increasing skin lesions consisting of confluent nodularity of the subcutaneous tissues of the anterior chest and abdomen and discrete nodules on the inner aspect of the left arm, and gastrointestinal complaints of anorexia, nausea, vomiting, cramps and ultimately obstipation.

In the first patient, amyloidosis was found in the walls of arteries of every organ examined, including the vasa vasorum of the aorta. The cerebral vessels were spared. The heart was dilated and there was moderate ventricular hypertrophy. The coronaries were patent throughout. Nodular deposits of amyloid were present in the subendocardium of both sides of the interauricular septum and of the left auricle. Amyloid was demonstrated in the intramyocardial vessels but none in the ventricular muscle itself. Focal areas of myocardial degeneration and fibrosis were present in both ventricles. The heart of the second patient was grossly normal except for left auricular endocardial thickening as a result of nodular infiltrations of amyloid beneath the endocardium. In addition there were scattered foci of amyloid in the epicardial fat and connective tissue septa around muscle fibers of the left auricle and both ventricles.

Both patients had gastrointestinal amyloidosis, the first one principally of blood vessels, the other of both blood vessels and intestinal musculature from esophagus to rectum. Scalp biopsy of the older patient revealed amyloid in the stroma around hair follicles and sebaceous glands. In the other patient there were amyloid deposits in subcutaneous tissues as well as discrete and confluent deposits of amyloid in the connective tissue of the subcutaneous fat.

This report again notes the clinical and pathologic similarity of primary systematized amyloidosis and the amyloid associated with multiple myeloma.

CORTELL

Ware, G. W. and Conrad, H. A.: Diverticula of the Pericardium. Am. J. Surg. **88:** 918 (Dec.), 1954.

The authors review cases of pericardial diverticulum in the literature and add one of their own. The ages of the patients range from 24 to 75 years. Symptoms associated with the disorders were not found helpful in making the diagnosis. Roentgenology was the most valuable preoperative study. A smooth round mass was generally noted in either hilum on a plain chest film. Its contour was found to change during respiration, being long and narrow in inspiration and short and broad in expiration. Microscopic examination of the lesions generally revealed the wall to be composed of loose connective tissue, with the lining of the cyst of endothelial or mesothelial origin.

ABRAMSON

Tricot, A., Baillet, J. and Helmcke, G.: An Observation of Constrictive Pericarditis Subsequent to X-ray Therapy. Arch. mal. coeur **47:** 922 (Dec.), 1954.

A 57-year-old woman is described who developed recurrent congestive heart failure following intensive radiation therapy for metastases to the spine and ribs of a breast cancer. She succumbed after 10 years of observation. The clinical symptomatology was that of constrictive pericarditis.

At autopsy, the pericardium was thickened to an average of 4 mm. The heart by itself was microscopically normal except for ischemic alterations of the subendocardium of the left ventricle. Histologically, a few carcinoma cells and infiltration with inflammatory cells was found within the pericardium. This chronic pericarditis is ascribed by the authors entirely to the radiation therapy which consisted in application of 13,000 r concentrated, from three directions upon the precordial region. Despite the development of the severe pericardial reaction and its consequences, the case is considered a therapeutic success because of the patient's 10 year survival after detection of the metastases.

PICK

Mendelow, H. and Genkins, G.: Studies in Myasthenia Gravis: Cardiac and Associated Pathology. J. Mt. Sinai Hosp. **21:** 218 (Nov.–Dec.), 1954.

A pathologic study was made of 12 consecutive cases of myasthenia gravis in whom postmortem examinations were obtained during the past five years at the Mount Sinai Hospital. Three of the cases studied had malignant thymomas, one had a benign thymoma and three cases showed persistent thymus tissue. Six of the 12 cases showed histologic alteration of the myocardium, ranging from scattered focal atrophy and vacuolization of the myofibrils, with accompanying slight lymphocytic infiltration of the connective tissue septums (resembling lymphorrhages) to severe, extensive myocardial necrosis. The latter was accompanied by abundant inflammatory reaction, consisting of polymorphonuclear leucocytes, lymphocytes, and mononuclear cells, with occasional multinuclear "giant" cells. The severer forms of myocardial involvement were found in the cases with thymic tumors, benign or malignant.

Seven of the cases showed striated muscle involvement, the milder ones having the classical small "lymphorrhages." However, in four of the cases actual necrosis of muscle fibres with secondary inflammatory reaction of varying intensity was present. The more severe forms of striated muscle involvement were seen in the cases manifesting severe myocardial damage.

There were no clinical aberrations of the cardiovascular system during life in the patients in this series, although thorough clinical and electrocardiographic study was not made in each patient. However, patients with definite myocarditis at autopsy had normal electrocardiograms during life.

CORTELL

PHARMACOLOGY

Silver, S., Newburger, R. A., Yohalem, S. B. and Feitelberg, S.: Method for the Determination of Radioiodine Levels in Blood Plasma. J. Mt. Sinai Hosp. **21:** 294 (Jan.–Feb.), 1955.

The purpose of the method is the determination of the concentration of radioiodine (I^{131}) in the plasma three days after a tracer dose, this concentration being expressed in per cent of the administered dose per liter of plasma. Carrier free radioactive iodine is used for the tracer dose and the standards. A well-type scintillation counter of such a size is used so that a 4 ml. sample of liquid in the test tube is completely contained within the well. Twenty-five to 100 microcuries of I^{131} are administered by mouth in 100 ml. of water and the exact dose recorded. Seventy-two hours after the tracer dose, 10 ml. of blood are drawn by venepuncture and oxalated. Four ml. of plasma are used for the determination of radioactivity, correction being made for decay from the time of administration of the tracer to the time of measurement. If the sample has a concentration in excess of 0.26 per cent of the administered dose per liter, it is necessary to determine the protein-bound radioiodine (PBI^{131}), which is done by precipitation with trichloroacetic acid in the same test tube, washing to eliminate the inorganic I^{131} and redissolving in 2M sodium carbonate or hydroxide and determining the radioactivity. Values of PBI^{131} above 0.27 per cent of the administered dose per liter are considered indicative of hyperthyroidism.

An analysis of a group of patients composed of 400 euthyroids and 100 hyperthyroids has shown that by the use of the method described a correct diagnosis could be made in 98.5 per cent of the cases.

CORTELL

Dirken, M. N. J., Gevers, F., Heemstra, H. and Huizing, E. H.: A Study of Defibrillating Agents

Perfused Rabbit Hearts. Circulation Research 3: 24 (Jan.), 1955.

The authors induced ventricular fibrillation in the perfused isolated rabbit heart by electric stimulation and tested the efficiency of various methods in restoring normal rhythm. Injections of acetylcholin were not successful in any experiment. Variable results were obtained by (a) arresting the coronary perfusion, (b) infusion of adenosin triphosphoric acid (ATP), (c) injection of potassium and calcium, or (d) electric defibrillation. Consistently good results were obtained by cooling the heart by lowering the temperature of the perfusing fluid. Subsequent rewarming increased the frequency and force of the beats and restored normal rhythm.

SAGALL

Badeer, H.: Influence of Oxygen on Hypothermic Cardiac Standstill in the Heart-Lung Preparation. Circulation Research **3**: 28 (Jan.), 1955.

Studies were undertaken to determine whether or not the cessation of the heart beat that follows severe hypothermia results from hypoxia of the myocardium. In experiments upon denervated dog heart-lung preparations, it was found that the presence of increased oxygen physically dissolved in the blood did not lower the critical hypothermic temperature producing ventricular fibrillation. The author concludes, therefore, that hypoxia of the myocardium is not a factor leading to hypothermic fibrillation of the ventricles in these preparations.

SAGALL

Steinkamp, R., Moore, C. V. and Doubek, W. G.: Thrombocytopenic Purpura Caused by Hypersensitivity to Quinine. J. Lab. & Clin. Med. **45**: 18 (Jan.), 1955.

In this case report of thrombocytopenic purpura in a 31-year-old woman sensitive to quinine hydrobromide, the authors note that they were able to produce a prolonged bleeding time, petechiae, and thrombocytopenia in a normal volunteer by the concomitant administration of oral quinine and intravenous injection of plasma from the sensitive patient.

The serum factor was resistant to prolonged storage at −10 C. In vitro platelet agglutination tests were positive in this patient only when quinine was added. The authors suggest that the antigen to which antibody is produced is a complex composed of a union between the drug and platelets.

WAIFE

Blumgart, H. L., Freedberg, A. S. and Kurland, G. S.: Treatment of Incapacitated Euthyroid Cardiac Patients with Radioactive Iodine. J.A.M.A. **157**: 1 (Jan. 1), 1955.

Medical treatment successfully alleviates discomfort and provides comfort for most patients with angina pectoris and congestive failure. There are a group of perhaps less than 5 per cent who remain disabled and in great discomfort despite medical treatment. Records of 1,070 euthyroid patients falling in this small 5 per cent, each of whom had been incapacitated for months or years and each of whom was treated with I^{131}, were collected from 50 clinics throughout the United States. Of 720 patients with angina pectoris (approximately 200 also had evidence of congestive heart failure), 76 per cent showed worthwhile improvement. Three hundred and fifty patients with congestive failure alone showed improvement in 62 per cent of the cases treated. Patients with angina pectoris who may be expected to gain the greatest benefits from treatment with I^{131} are those in whom the disease has been relatively stationary, or only slightly progressive, over a period of one year or more. Patients with congestive failure should show some evidence of cardiac reserve, such as improvement in signs of congestive failure and other symptoms, on bed rest or with the use of diuretics and digitalis. The basal metabolic rate in patients should be more than minus 10 per cent, and the patient should be alert, cooperative and emotionally stable. However, hyperactive tense patients are particularly favorable candidates. In the clinical management of these patients, small daily doses of thyroid are administered to maintain the lowest metabolic rate consistent with comfort. In intractable cardiac cripples who are usually considered for surgery, hypothyroidism induced by radioactive iodine gives improvement through medical means without the risk of surgical complications.

KITCHELL

Robinson, H. M., Sr.: A Medical Treatment for Stasis Ulcers. J.A.M.A. **157**: 27 (Jan. 1), 1955.

The author studied the effect of local antibiotic powders and dry dressing in a series of 72 patients with stasis ulcers of the legs. Only three subjects were resistant to treatment, primarily because the medication caused a dermatitis. The substances used were chloramphenicol, bacitracin, sulfanilamide, diphenmethanil methylsulfate, chlortetracycline, oxytetracycline, erythromycin, and bacitracin-polymyxin B sulfate.

The application of the powders permitted the production of granulation tissue and healing of the ulcers in most instances. There was a tendency in some patients for the lesions to recur or for new ones to form, but these responded to further powder treatment. The greatest drawback of the therapy was the cost of the drugs.

ABRAMSON

Weinberg, S. J. and Haley, T. J.: Centrally Mediated Effects of Cardiac Drugs: Strophanthin-K, Quinidine and Procaine Amide. Circulation Research **3**: 103 (Jan.), 1955.

The extracardiac sites of action of strophanthin-K,

quinidine sulfate and procaine amide were studied by the injection of varying doses of these drugs into the third ventricle of unanesthetized mongrel dogs.

The intraventricular injection of strophanthin-K produced a variety of cardiac irregularities including paroxysmal ventricular tachycardia. Intravenous administration of equal or larger doses on later occasions or in other dogs did not cause these cardiac irregularities. Similar findings were likewise observed following the intraventricular injection of quinidine. Again these were not seen after the intravenous administration of equal or larger doses of the drug. The centrally induced cardiac effects of these drugs were accompanied by autonomic manifestations resembling those seen in patients with digitalis or quinidine intoxication.

The arrhythmic effects of intraventricular strophanthin-K could be prevented by the intraventricular injection of either quinidine or procaine amide which induced anesthesia (stage III, plane II); they could be terminated or modified by intravenous quinidine sulfate, procaine amide or sodium pentobarbital; and they could be entirely blocked by intravenous hexamethonium chloride.

SAGALL

Russek, H. I., Zohman, B. L. and Dorset, V. J.: Objective Evaluation of Coronary Vasodilator Drugs. Am. J. M. Sc. **229:** 46 (Jan.), 1955.

This report presents the results obtained in a five year study of the effect of 16 different agents on the electrocardiographic response to standard exercise tests in patients with coronary insufficiency. It was found that glyceryl trinitrate in therapeutic doses exerts a favorable effect upon the response to exercise as recorded electrocardiographically. Papaverine in doses of 1 to 2 grains intravenously or 3 to 8 grains orally is effective in abolishing the abnormal response to exercise. Such benefit was not observed with the usual therapeutic doses. The results obtained with Metamine (trinitrate biphosphate), Paveril, and Nitroglyn were unsatisfactory. Unimpressive effects were observed with the use of Aminophylline, Roniacol, Priscoline, tetraethylammonium chloride, Octyl nitrate, Khellin, heparin and Dicumarol when tested by this method. Ethyl alcohol and morphine, although effective in modifying pain, did not improve the exercise response in these patients. Of all agents tested, Peritrate remains the most effective drug tested for prolonged prophylactic therapy in angina pectoris. A 10 to 20 mg. dose afforded protection for 4 to 5 hours as judged by the two step test in the majority of patients studied.

SHUMAN

Gamble, J. R., Dennis, E. W., Coon, W. W., Hodgson, P., Willis, P. W., MaCris, J. A. and Duff, I. F.: Clinical Comparison of Vitamin K_1 and Water-Soluble Vitamin K. Ann. Int. Med. **95:** 52 (Jan.), 1955.

The prothrombin responses to water and to oil-soluble vitamin K preparations in patients under treatment with anticoagulants is compared. It is shown that oil-soluble vitamin K, is more effective than any other agent now available in combating drug-induced hypoprothrombinemia. In contrast, the water-soluble vitamin K preparations are unreliable and have an inconstant effect. In most cases vitamin K, in doses as low as 1 to 5 mg. orally has been observed to produce as satisfactory a response, in as short a time as four hours, as the large intravenous doses generally recommended.

In the event of severe bleeding due to oral anticoagulants, intravenous vitamin K, in a dose of at least 10 to 50 mg. is recommended in addition to whole blood or plasma transfusions, if the latter are necessary to combat shock. The dose must be individualized, with consideration given to source and severity of bleeding and reason for use of anticoagulant therapy. The smaller dose should be adequate when bleeding is moderate and resumption of therapy is planned. In hypoprothrombinemia due to absorptive difficulties water-soluble vitamin K substances or vitamin K, appear to be equally effective, the latter in amounts as small as 5 mg. intravenously.

BERNSTEIN

Ruskin, A.: Acetazoleamide (Diamox) Diuresis. Arch. Int. Med. **95:** 24 (Jan.), 1955.

Acetazoleamide diuresis is associated with carbonic anhydrase inhibition in the renal tubules, producing an alkaline urine, excessive distal tubular excretion of potassium, and decreased tubular reabsorption of sodium and other cations, bicarbonate, and, consequently, water. Lack of toxicity in the heart and kidney is evidenced by failure to inhibit the activity of succinic dehydrogenase and adenosine triphosphatese in those organs. Such hemodynamic alterations as may occur after acetazoleamide administration do not contribute to its diuretic effect.

BERNSTEIN

Greeley, H. P., Smedal, M. I. and Most, W.: The Treatment of the Carotid-Sinus Syndrome by Irradiation. New England J. Med. **252:** 91 (Jan. 20), 1955.

The authors describe the results of treatment of 56 patients with carotid-sinus syndrome with irradiation over a period of fourteen years. The follow-up period was too short for adequate evaluation in 4 patients but the remaining 52 had spontaneous attacks of syncope, episodes reproduced by the examining physician and follow-up periods twice the length of any spontaneous remission. Medical treatment had not been sufficient to produce remissions. The total dose of irradiation to the affected sinus area was 500 r if unilateral and 400 r if bilateral. The average follow-up period was 3.3 years with the longest remission 14 years. Complete remission occurred in 58 per cent and an additional 12 per cent

were moderately benefited. The mechanism of relief is unknown but it is believed that it may be by depression of nerve endings. There were no complications as a result of treatment.

ROSENBAUM

Welch, J. W.: Intravenous Vasopressors in Surgical Shock. Am. J. Surg. **88:** 922 (Dec.), 1954.

The author reported the effect of intravenous Arterenol or Neo-synephrine in the treatment of surgical shock in a series of 50 patients. The drugs were given by continuous slow infusion in a concentration of 4 mg. per ml. This was obtained by the addition of 4 mg. to 1 liter of a suitable vehicle. The rate of administration was such as to maintain the blood pressure at the desired level.

A satisfactory pressor response was obtained in all cases in which Arterenol was used and in 84 cases of the Neo-synephrine group. The results were found encouraging enough to justify further careful clinical observation and evaluation.

ABRAMSON

PHYSICAL SIGNS

Weitzman, D.: The Mechanism and Significance of the Auricular Sound. Brit. Heart J. **17:** 70 (Jan.), 1955.

Intracardiac pressure studies of 12 individuals with congenital heart disease were used to detect timing of the auricular sound in relation to pressure changes. Phonocardiographic recordings indicate that the auricular sound has a double appearance, the first part of which is inaudible and is attributed to the muscular action of the auricle because it is related in time to the rise of pressure in the auricle. The second portion is audible and is attributed to a filling sound produced by blood entering the ventricle from auricular systole.

An auricular sound was audible in the twelve patients with congenital heart disease, 46 with hypertension, 29 with cardiac infarction, 4 with aortic valve lesions and 9 with heart block. The clinical electrocardiographic and radiologic findings in this group were compared to 100 with normal hearts, 86 with hypertension, 16 with recent and 62 with old infarctions and 42 with aortic stenosis all of whom did not have an audible auricular sound.

The auricular sound is not heard in health. It is especially audible in left ventricular hypertrophy of hypertensive origin but not of aortic valve origin. It may be heard in the presence or absence of heart failure. Persistence of this sound after infarction is an unfavorable sign.

SOLOFF

Luisada, A. A. and Gamna, G.: Clinical Calibration in Phonocardiography. Am. Heart J. **48:** 826 (Dec.), 1954.

The authors introduce a new and simple device for calibration of heart sounds and murmur based on the production of a sound vibration of known amplitude and frequency over the chest wall and its transmission to the microphone. Clinical experiments in reference to best location for placing the calibrator and the transmission of the signal to various areas of the precordium area described. The experimental production in dogs of either pneumothorax or pulmonary effusion was used to study the effect of the presence of fluid or air in the pleural cavities on the signal. The authors discuss the merits of the sound signal in phonocardiography as compared with the electric signal.

RINZLER

PHYSIOLOGY

Hoff, H. E. and Geddes, L. A.: Potential Changes in the Heart Caused by Cooling. J. Appl. Physiol. **7:** 416 (Jan.), 1955.

With the application of body cooling for cardiac surgery, the cardiac changes produced by this procedure assume great clinical importance. Various electrocardiographic changes occur in the cooled zone. These changes include a progressive lengthening of the Q-T interval and a growing inversion of the T wave denoting a progressive retardation of repolarization. Further cooling causes an R wave of increased amplitude and width indicating retarded activation. Single or repetitive extrasystoles arising in the cooled zone may lead to ventricular fibrillation. As cooling proceeds and especially if the temperature of the water falls below 10 C., an elevation of the S–T segment develops. This paper is a study of this phenomenon.

Copper thermode leads in direct contact with the heart were used to record chest leads in deeply anesthetized dogs. Curare was used to eliminate artifacts caused by somatic activity. In some animals the esophagus and stomach were removed to avoid artifacts. Local areas of the myocardium were cooled. Temperatures of 10 to 15 C. in the fluid flowing through the thermode were necessary to produce changes in the S-T segment. The sequence was as follows, inversion and prolongation of T wave, increase in amplitude of R and then delay in intraventricular conduction. A monophasic electrogram occurred indicating that cooling can almost completely disable the responsive mechanism. Elevation of the S-T segment does not occur until the broadening T wave encroaches on the complex of the next beat. This result suggested that the cooled tissue responds to a new beat before full recovery from the preceding one, so electric balance is achieved at a level above that at which the R wave began. Therefore, S-T elevation may not represent injury or unresponsiveness but may represent the ability of the heart to carry from one cycle to another a continuum of potential imbalance resulting from the fact that each beat is followed by another without time for complete electric recovery.

In order to test the validity of this concept the

heart was slowed by vagal stimulation. This extra time for recovery allowed the S-T segment to return toward normal. However, prostigmine stimulation of the vagus slowed the heart but did not depress the elevated S-T segment.

Cooling of the myocardium slows recovery, impairs conduction and, if continued, causes a reversible diastolic depolarization of the cooled area. Each of these factors may be responsible for the S-T segment displacement. Application of these concepts to electrocardiographic changes caused by ischemia is suggested.

WECHSLER

Holland, W. C. and Dunn, C. E.: Role of the Cell Membrane and Mitochondria in the Phenomenon of Ion Transport in Cardiac Muscle. Am. J. Physiol. **179**: 486 (Dec.), 1954.

Membrane permeability of the intact cell is affected by cholinergic compounds, anesthetics and cardiac glycosides in a rapid and reversible manner. The functional state of the cell is changed and permeability to Na and K is altered. Ion transfer in isolated mitochondria is largely unchanged under the influence of similar agents. On the other hand such metabolic inhibitors as dinitrophenol, malonate and fluoroacetate effect ion permeability of intact cells and isolated mitochondria in a similar fashion. The authors make the following suggestion: permeability phenomena of short and transient nature, nerve impulses, muscle conrtaction and anesthesia, are concerned with membrane permeability changes but slower metabolic ionic changes in resting or basal states and recovery are related to the properties which reside in mitochondria.

OPPENHEIMER

Allison, P. R. and Linden, R. J.: Bronchoscopic Approach for Measuring Pressure in Left Auricle, Pulmonary Artery, and Aorta. Lancet **1**: 9 (Jan. 1), 1955.

Extending their previously described technic for left atrial puncture, the authors describe puncture of the pulmonary artery through the anterior wall of the trachea just above the carina and of the aorta at a site 2 to 3 cm. higher in the trachea. Typical pressure curves are demonstrated. The authors suggest that in mitral disease the technic is useful in the differentiation between stenosis and regurgitation, in following the postoperative course, in distinguishing restenosis or inadequate dilatation from other factors responsible for unfavorable course, and in distinguishing those patients in whom mitral obstruction is not the major cause of the symptoms. In 59 of 61 patients, the forecast of finding at operation (as to the presence or absence of regurgitation) was correct. No illness or death was encountered in the 121 patients in whom the procedure was performed.

MCKUSICK

Berson, S. A. and Yalow, R. S.: Critique of Extracellular Space Measurements with Small Ions; Na^{24} and Br^{82} Spaces. Science **121**: 34 (Jan. 7), 1955.

Curves showing the fraction of total Na^{24} or Br^{82} in the body per liter of plasma, expressed over 24 hours or more, have multiple components. Between 15 minutes and one hour after intravenous administration, the concentration decreases almost exponentially with a shallower slope than in the early phase (0 to about 15 minutes). The earliest curve probably represents mixing in the extracellular fluid, while the second phase is attributable to penetration into cells or bone. Assuming that intracellular penetration proceeded at the same rate throughout the first period as during the second, the extracellular fluid volume could be obtained by zero time extrapolation of the second phase.

Estimations in man seem to bear out these concepts. The results are reproducible and are in good agreement with results obtained by inulin or sucrose. In edematous subjects, however, values derived from the extrapolation of the slow component underestimates the true extracellular space because of slow equilibration.

In nonedematous subjects small, freely diffusible ions distribute into a large but not complete volume of the extracellular fluid within 15 or 20 minutes. Some intracellular sites probably have also been penetrated by this time. These values, which cannot be considered a precise measure of extracellular fluid, are grossly in error when this fluid volume is markedly increased.

WAIFE

Ashworth, D. and Nahum, L. H.: Auricular Excitability of the Normal Dog Heart. Yale J. Biol. & Med. **27**: 168 (Dec.), 1954.

Electrodes were permanently implanted on the auricles of dogs to permit study of the excitability cycle in a normal physiologic environment. The curves obtained soon after implantation were uninfluenced by injury effects as substantiated by histologic studies. The auricular electrograms showed a QRS, S-T segment and a T wave. The curves of excitability were all similar, showing an absolute refractory period, a relative refractory period with a smoothly declining slope, and a constant diastolic threshold level. Total refractory period had about the same duration as the auricular electrogram. The recovery period in the auricle was shorter than in the ventricle, a finding which is probably due to the same factor which causes faster conductivity in the auricle. A super-normal period was clearly demonstrated in 18 per cent of the cases. This may have been due to some alteration of the normal physiologic state by the manipulations.

ENSELBERG

RHEUMATIC FEVER, RHEUMATIC HEART DISEASE, COLLAGEN DISEASES

Attal G.: Biological Test in Bouillad's Disease. Arch. mal coeur **48**: 60 (Jan.), 1955.

Comparative studies concerning the diagnostic value of various laboratory tests in acute rheumatic fever and its complications are reported. None of the laboratory procedures is specific for the disease and only one, an elevated sedimentation rate, is found in all instances. A normal sedimentation rate rules out active rheumatic fever whereas a greatly accelerated sedimentation rate does not permit exclusion of other diseases like rheumatoid arthritis, Still's disease, bacterial endocarditis and osteomyelitis. The blood fibrinogen level becomes diagnostic if it exceeds 8 Gm. per 1000 cc. Additional laboratory confirmation is obtained by finding an increase of α_2-globulines with γ-hyperglobulinemia. An elevated antistreptolysin and antihyaluronidase titer is of help in the differential diagnosis because neither a bacterial endocarditis, a viridans infection nor chronic forms of polyarthritis lead to their elevation. The diagnostic problem is, however, very great when a subacute bacterial endocarditis develops on top of active rheumatic fever. Chorea may or may not show the same abnormal laboratory findings as rheumatic polyarthritis. In the presence of a normal sedimentation rate and a fibrinogen level under 5 Gm. occurrence of cardiac complication of chorea is very unlikely.

Biologic tests are of utmost importance in the evaluation of rheumatic activity when clinical manifestations have subsided. Most valuable in this respect are the determination of blood protein fractions and in particular the sedimentation rate which permits quick recognition of clinical silent bouts of reactivation.

PICK

McEwen, C.: The Treatment of Rheumatic Fever. Am. J. Med. **17**: 794 (Dec.), 1954.

The use of antibiotics, cortisone, corticotropin and salicylates in the treatment of rheumatic fever is discussed. Penicillin is important to use to eliminate the hemolytic streptococcal carrier state as well as to prevent such infections in patients who have recovered from rheumatic fever. Although the value of cortisone and corticotropin in rheumatic carditis is not yet established beyond question, present evidence is encouraging, especially when therapy can be started within a few days of onset of illness. These hormones are of little benefit in long-standing subacute and chronic carditis. The value of salicylates in carditis is still less clear but the meagre evidence is sufficiently hopeful to warrant the combined use of this drug with cortisone. Salicylate is preferable to cortisone or corticotropin for the treatment of rheumatic polyarthritis without evidence of carditis.

A plan of treatment is suggested. Penicillin should be given at once in sufficient doses to eradicate the hemolytic streptococcal carrier state in any patient with rheumatic fever. Prophylaxis should then be begun and continued indefinitely to prevent further infection with hemolytic streptococci. In the absence of carditis, salicylate alone is preferable to hormone therapy. If C-reactive protein has not disappeared by the end of four weeks, it is probable that the patient has smoldering carditis and cortisone is indicated. In the presence of carditis, 300 mg. of cortisone daily by mouth should be started at once. After six weeks the dose is reduced to half a tablet (12.5 mg.) daily. Further treatment is indicated if C-reactive protein is still present after six weeks. A transient rebound, when hormone is stopped, does not call for further treatment. If a true relapse occurs or if clinical or laboratory evidence of continuing lowgrade carditis persists, cortisone should be resumed. To minimize the rebound phenomenon it is advisable to continue salicylate dosage at a level of 0.03 Gm. per pound of body weight daily for three weeks after cortisone has been stopped.

HARRIS

Zilli, A., and Gamna, G.: Evolution of Murmurs in Early Rheumatic Heart Disease. Am. J. Med. **17**: 775 (Dec.), 1954.

A clinical and phonocardiographic study, made in 43 patients at the first attack of rheumatic fever, was repeated until either recovery or a definite chronic course was evident. Twenty patients had systolic murmurs at the apex, pulmonic or aortic areas at the first observation. The murmurs decreased or disappeared in one-half and increased in the other half of the patients. One-third of the basal systolic murmurs were transmitted; two-thirds were of aortic or pulmonic origin. A significant pulmonic systolic murmur was present in one-half of the cases in the beginning, in one-fourth at the end. A significant aortic systolic murmur was present in one-fifth of the cases at the beginning and end of observations. Thirteen cases with a systolic and diastolic murmur at the apex were all severe. At the end of observation nearly two-thirds showed no further evidence of the diastolic rumble. Four cases had an apical systolic and an aortic diastolic murmur at first observation. The aortic diastolic murmur subsequently decreased in one case and persisted or increased in the others. Four cases had minimal, diffuse murmurs.

In comparison with auscultation, phonocardiography presents the advantages of: (1) giving objective proof of the existence of murmurs, extrasounds or both; (2) allowing gross evaluation of the intensity of a murmur through electric and clinical calibration; (3) giving a picture of the "shape" and "aspect" of the murmur; (4) confirming the complete disappearance of a murmur.

HARRIS

Zinsser, H. F. Jr.: The Selection of Patients for Mitral Commissurotomy. Am. J. Med. **17:** 804 (Dec.), 1954.

Mitral commissurotomy should be restricted to patients with significant and progressive disability due to mitral stenosis. Its use in asymptomatic patients is not justified because of the present surgical risk (3–5 per cent in better risk patients). The technical success depends upon the surgeon's experience with this procedure. A given patient can be improved only to the degree that his cardiovascular disability is caused by simple mechanical obstruction at the mitral valve. With good surgery and proper medical evaluation many patients have improved, at least on a short term basis. The ideal patient is one with "pure" mitral stenosis whose disease has progressed only to the stage of pulmonary congestion. Mitral commissurotomy is less satisfactory in patients whose disease had advanced beyond the phase of pulmonary congestion and into the stage of "right heart failure." In patients over fifty years of age the surgical risk is increased but gratifying results have been achieved in a number of older patients. Active rheumatic fever or carditis is an absolute contraindication to mitral commissurotomy. Auscultation is unreliable in evaluating patients with prominent apical systolic murmurs since this does not guarantee the presence of a significant mitral regurgitation. Often, despite a loud apical systolic murmur, the patient is found to have severe mitral stenosis without significant insufficiency and has derived considerable benefit from mitral commissurotomy. All such patients deserve the benefit of special study, including an angiocardiogram, before a final decision is reached. Aortic and tricuspid valvular disease need not disqualify a patient from surgery under certain conditions.

HARRIS

Adams, F. H.: Newer Concepts in the Diagnosis and Treatment of Rheumatic Fever. J.A.M.A. **156:** 1319 (Dec. 4), 1953.

In the development of rheumatic fever certain factors appear to be of importance. Listed in the order of their apparent importance, they are (1) streptococcic infections, (2) hereditary predisposition, (3) environment (stress), (4) endocrine status (adrenal), and (5) dietary intake and nutritional status. Rheumatic fever has its peak incidence at 9 years of age and is rare under 5 years of age, but may occur at all ages. Approximately 2 to 3 per cent of streptococcic infections give rise to rheumatic fever. The treatment should be directed towards eradication of existing streptococcic infection, prevention of future invasion of the body by streptococci, rest, suppression of symptoms, provision of a well-balanced diet and gradual resumption of activity after all signs of active disease have disappeared. Once the disease has become inactive, recurrent attacks may be prevented by preventing streptococcic infections. This can be accomplished by the administration of 0.5 to 1 Gm. sulfadiazine daily, or by oral administration of 200,000 units of penicillin twice a day. Prophylaxis should probably be continued for five years after the last attack or until adolescence, whichever occurs first.

KITCHELL

Luisada, A. A.: Recent Advances in the Diagnosis of Rheumatic Heart Disease. Am. J. Med. **17:** 781 (Dec.), 1954.

The diagnosis of rheumatic heart disease requires recognition of the etiology of the process and evaluation of myocardial, endocardial and pericardial lesions, as well as of possible lingering activity of the rheumatic process. The history and physical examination often answer the question whether the patient is a rheumatic; the electrocardiogram frequently establishes myocardial damage; various laboratory tests and clinical findings help in the diagnosis of activity. Murmurs should be evaluated carefully. The differential diagnosis between the apical diastolic murmur of mitral stenosis and that of "relative" stenosis caused by carditis is aided by phonocardiography. The differentiation between "pure" mitral stenosis and mitral insufficiency plus stenosis may be necessary in relation to possible surgical repair of the valve. The following diagnostic methods are reviewed: (1) physical examination and low frequency tracing, (2) auscultation and phonocardiography; (3) electrocardiography and vectorcardiography; (4) ballistocardiography; (5) pressure tracings of the left atrium; (6) esophagocardiograms; (7) roentgenograms and roentgenkymograms; (8) electrokymograms. "Pure" insufficiency or stenosis is recognized without difficulty by means of physical data plus electrocardiography, phonocardiography and roentgenology. Demonstrations of associated mitral insufficiency in a case of mitral stenosis may be difficult and use of various subsidiary diagnostic methods may be necessary.

In mitral insufficiency a ventricular pressure pattern (positive plateau-like wave) is transmitted to the left atrium. Esophagocardiography, roentgenkymography, electrokymography, direct measurements of atrial pressure and digital exploration permit recognition of this abnormal pressure wave which causes systolic expansion of the atrium.

The various technical aids for diagnosis of associated aortic, pulmonic and tricuspid defects are discussed.

HARRIS

McMillan, I. K. R.: Aortic Stenosis. Brit. Heart J. **17:** 56 (Jan.), 1955.

A cinematographic study of motion of the aortic valve produced by an artificial pump is made of 30 stenosed aortic valves and the effect of post mortem valvotomy in 25 and of valvotomy in life in six. The uncalcified stenotic valve can be easily divided.

Forceful dilatation may damage a mobile cusp if the other two are fused. Gross calcification militates seriously against a successful functional operative result.

SOLOFF

Brock, G.: When Should Mitral Stenosis be Operated Upon? Cardiologia **26:** 21 (Fasc. 1), 1955.

An attempt is made to estimate the number of cases which might be considered potential candidates for mitral surgery. The calculations indicate that about 1.5 person per thousand of the Swedish population, about 10,000 cases, have mitral stenosis. This figure is lower than that presented by others, in particular by Wood for Great Britain.

Two factors will have a great influence on the magnitude of this surgical problem: the limitations of indications to surgery, and the spreading of knowledge concerning the feasibility of the operation among physicians and laymen. A further important factor will be the decision concerning early operation on asymptomatic patients. A review of the literature reveals that, at present, opinions vary concerning advisability of surgery at this stage of the disease.

PICK

Mozziconacci, P. and Caramian, M. K.: Results of Treatment with Hormones in Acute Rheumatic Fever. Arch. mal. coeur **48:** 3 (Jan.), 1955.

Method and results of hormonal treatment in 267 cases of acute rheumatic fever are reviewed with one year followup. The authors preferred cortisone and used the following doses: 100 mg. daily for children under 5; 150 mg. for children between 5 and 10; and 200 mg. for children between 10 and 15. In the first 48 hours an additional dosage of 50 mg. per day was also given. The average length of treatment was 15 days; in severe cases, it was continued from 2 to 4 weeks longer, until the sedimentation rate was under 20 mm. per hour.

In 23 cases with severe carditis and congestive failure, a good result was obtained in 17 while six children died. In a second group of patients, 131 cases, with carditis but without cardiac failure, 125 responded favorably while 6 died from cardiac failure, despite therapy. In another group of 113 cases with no cardiac involvement on admission, only 2 presented minimal symptoms at the time of discharge.

The authors conclude that cortisone should be the drug of choice for treatment of rheumatic fever with or without carditis.

LUISADA

Owen, S. G. and Wood, P.: A New Method of Determining the Degree or Absence of Mitral Obstruction: An Analysis of the Diastolic Part of Indirect Left Atrial Pressure Tracings. Brit. Heart J. **17:** 41 (Jan.), 1955.

The authors reason that, in the presence of obstruction to the forward flow of blood at the mitral orifice, the left ventricle fills slowly and inadequately despite the development of a large pressure head and flow tends to continue throughout diastole in contrast to mitral incompetence in which the combination of a high atrial pressure at the end of systole with no forward obstruction produces a rapid and early filling of the left ventricle. They therefore use the characteristics of the diastolic portion of the pulmonary artery wedge wave to determine whether mitral stenosis or incompetence is dominant when there is clinical evidence of both. The rate of fall (mm. Hg per second) of the diastolic portion of the pulmonary artery wedge wave divided by the height of the v wave expresses this relationship. A value greater than 1.6 is unlikely to occur in pure stenosis or one associated with trivial incompetence.

SOLOFF

Schwab, J. H., Watson, D. W., and Cromartie, W. J.: Further Studies of Group A Streptococcal Factors With Lethal and Cardiotoxic Properties. J. Infect. Dis. **96:** 14 (Jan.–Feb.), 1955.

Previous studies had shown that a reaction resembling the generalized Schwartzman phenomenon could be produced with soluble products of group A streptococci. Intravenous injection of an extract of a streptococcal skin lesion, followed by a second intravenous injection of either a filtrate of a culture of *Salmonella typhosa* or a reduced culture filtrate of streptococci which had a high titer of streptolysin O, produced a reaction, the prominent features of which were death and necrosis of cardiac muscle, the latter being described as myofiber necrosis.

Further studies reported here, give strong although indirect evidence that streptolysin O is the active provoking factor in the reduced filtrate. Some of the properties of the factor produced in the streptococcal lesion which potentiates the activity of streptolysin O were also demonstrated. The active material is produced by many but not all strains of group A streptococci and is heat labile, withstands lyophilization and may be of large molecular size.

CORTELL

Kelley, V. C., Ely, R. S., Done, A. K. and Ainger, L. E.: Studies of 17-Hydroxycorticosteroids. VI. Circulating Concentrations in Patients with Rheumatic Fever. Am. J. Med. **18:** 20 (Jan.), 1955.

Plasma 17-hydroxycorticosteroid concentrations measured in patients during various phases of rheumatic fever activity were elevated early in the course of acute rheumatic fever and decreased as the disease progressed. Patients with well established active rheumatic fever, inactive rheumatic fever and Sydenham's chorea had circulating concentrations of these steroids, significantly lower than the control group. The finding of elevated plasma steroid levels in patients with early acute rheumatic fever is interpreted as indicative of a "stress response." The sub-

sequent depression of these steroid levels to abnormally low values during continuing rheumatic activity indicates a relative failure of the adrenal cortex to comply with demand. This, combined with the demonstrated ability of these patients to produce adequate elevations of steroid levels in response to exogenous ACTH, suggests that a "relative adrenal insufficiency" exists in patients with rheumatic fever. Existing data do not eliminate the possibility that the anterior pituitary rather than the adrenal cortex is to be implicated in the failure of patients with certain phases of rheumatic fever to maintain usual circulating concentrations of 17-hydroxycorticosteroids.

HARRIS

Vogl, A., Blumenfeld, S. and Gutner, L. B.: Diagnostic Significance of Pulmonary Hypertrophic Osteoarthropathy. Am. J. Med. **18:** 51 (Jan.), 1955.

Seven cases of pulmonary hypertrophic osteoarthropathy are presented in which the following classical features of the syndrome occurred: (1) Bone pain, which is acute in onset, deep-seated, burning in character and aggravated by lowering of the extremities; (2) stiffness of the fingers; (3) muscular weakness; (4) broadened or cylindrical appearance of the distal thirds of the extremities produced by a firm, hardly pitting edema; (5) redness, glistening, warmth and perspiration of the skin of the affected regions; (6) intense tenderness to pressure over the affected bones and pain on passive motion of the adjacent joints; (7) progressive clubbing and dusky discoloration of the tips of fingers and toes; (8) rapid disappearance of pain and swelling after successful treatment of the underlying process. Correct diagnosis is important for two reasons: (1) the condition is often very distressing and yields to no treatment other than elimination of the underlying primary disease; (2) it not only indicates the presence of serious disease of the lungs, particularly pulmonary carcinoma, but may precede the appearance of respiratory symptoms in pulmonary carcinoma by several months, and thus aid in its early diagnosis. Evidence is presented to support the view that abnormally increased peripheral blood flow plays a role in the pathogenesis of pulmonary osteoarthropathy. This derangement of peripheral circulation may be dependent upon some pathologic intrathoracic reflex which is promptly abolished by surgical removal of the affected lobe or of an extrapulmonary mass. Despite the identity of the anatomic changes in the hereditary types of congenital clubbed fingers and idiopathic hypertrophic osteoarthropathy with those of the "pulmonary" type of osteoarthropathy, the latter apparently is a separate morbid entity.

HARRIS

Taylor, H. E. and Strong, G. F.: Pulmonary Hemosiderosis in Mitral Stenosis. Ann. Int. Med. **42:** 26 (Jan.), 1955.

Focal accumulation of hemosiderin-containing phagocytes formed distinct nodules in the lungs of 42 per cent of cases dying with advanced mitral stenosis. In a further 31 per cent the lungs presented the more classic findings of brown induration. The nodular aggregates of siderophages are considered to be the end result of repeated small pulmonary hemorrhages caused by chronic venous congestion and pulmonary hypertension. The hemosiderin can be released from the phagocytes within the lung and impregnate the elastica and capillary basement membranes of the alveolar septa. Fragmentation of elastica may result, but fibrosis was not prominent. Such aggregates when sufficiently large are opaque to x-ray films and may appear as miliary densities in radiographs of the chest.

WENDKOS

Wallace, H. M. and Rich, H.: The Changing Status of Rheumatic Fever and Rheumatic Heart Disease in Children and Youth. Am. J. Dis. Child. **89:** 7 (Jan.), 1955.

A summary of current data available from the literature and data obtained from statistical reports of the New York City Health Department indicates that there has been a significant reduction in the number of deaths in children from rheumatic fever and rheumatic heart disease in the past decade. Of greater significance, however, is the finding from the New York City data that there are fewer children who develop rheumatic heart disease. This is statistically significant. Several factors are discussed concerning this change. The development, and widespread use of prophylactic antibiotic drugs is given the major share of credit for this decline.

HARVEY

Elster, S. K., Wood, H. F. and Seely, R. D.: Clinical and Laboratory Manifestations of the Postcommissurotomy Syndrome. Am. J. Med. **17:** 826 (Dec.), 1954.

The postcommissurotomy syndrome is characterized clinically by chest pain, fever and cough, often with signs of pleuritis and pericarditis. It has appeared as early as ten days after operation and has recurred as late as fourteen months postoperatively. Its incidence varied from 10 to 30 per cent in different reports. The authors report their experience with this syndrome. Ten of sixteen patients developed the postcommissurotomy syndrome ten days to seven months following mitral commissurotomy. Seven patients had multiple attacks. Bacteriologic studies yielded negative results. Penicillin prophylaxis was ineffective and antibiotics failed to modify the course. Salicylates appeared to abbreviate the illness. No significant change in the antistreptolysin-O titer occurred. The C-reactive protein was the most sensitive laboratory test for the postcommissurotomy syndrome and the most useful in management. The syndrome represents a self-

limited form of pericarditis and pleuritis induced by the trauma of surgery in patients with rheumatic heart disease. Salicylate suppressive therapy is recommended for all postcommissurotomy patients. The C-reactive protein test is suggested as a useful and sensitive test for the activity of the postcommissurotomy syndrome.

HARRIS

Wood, H. F. and McCarty, M.: Laboratory Aids in the Diagnosis of Rheumatic Fever and in Evaluation of Disease Activity. Am. J. Med. **17:** 768 (Dec.), 1954.

Although no specific diagnostic test for rheumatic fever exists and there is no reliable test for rheumatic activity when the patient is being treated, the laboratory may be helpful in the diagnosis of rheumatic fever and in guiding the medical management of the disease by providing an index of rheumatic activity. The demonstration of serum antibodies to individual antigens of group A streptococci has proved to be valuable for detecting the occurrence of recent streptococcal infections. The most practical and feasible test is the antistreptolysin O test. At least 80 to 90 per cent of patients with rheumatic fever have definite elevations in antistreptolysin titer early in the course of the disease. The limitations on the diagnostic usefulness of this test imposed by the fact that not all patients respond with significant increases of antibody to this antigen can be overcome by laboratories which can carry out tests for other streptococcal antibodies. A second limitation is that this test is not specific for rheumatic fever.

The time-honored test for rheumatic activity is the determination of the erythrocyte sedimentation rate. Because of its simplicity and relative reliability, it will continue to be the most widely used single test for rheumatic activity. Its limitations include insensitivity and a poorly defined range of normal. Alternate procedures employed for estimating rheumatic activity include: total leukocyte count, the Weltmann serum coagulation reaction, determination of serum mucoprotein, measurement of non-specific hyaluronidase inhibitor of serum, measurement of serum complement, determination of serum C-reactive protein, the bactericidal activity of the blood versus *Bacillus subtilis*, a serum precipitation reaction with a quaternary ammonium salt and a diphenylamine color reaction with serum.

The most widely used of these procedures at present is the determination of C-reactive protein in the serum. Except in cases of pure chorea, C reactive protein is always present in the serum in acute rheumatic fever and the amount is proportional to the severity of the illness.

HARRIS

Stollerman, G. H.: The Use of Antibiotics for the Prevention of Rheumatic Fever. Am. J. Med. **17:** 757 (Dec.), 1954.

The incidence and morbidity of rheumatic fever can be reduced significantly by appreciation on the part of physicians and the general public of the importance of early diagnosis and proper therapy of streptococcal disease and upon diligent protection of rheumatic subjects from streptococcal infection. There are two effective approaches to the prevention of rheumatic fever by the use of antibiotics. The first is protection of the highly susceptible rheumatic subject from repeated attacks of the disease by maintaining continuous chemoprophylaxis against new streptococcal infections. The second is prompt and adequate treatment of streptococcal pharyngitis in the general population to reduce the incidence of first attacks of rheumatic fever. The major limitation of the chemotherapeutic approach to the prevention of rheumatic fever is the difficulty of clinical identification of streptococcal sore throat. To avoid the promiscuous and unnecessary administration of penicillin to patients with viral and nonstreptococcal upper respiratory infections, the clinical criteria for the diagnosis of streptococcal pharyngitis should be more widely recognized. Simple coryza, cough, hoarseness and tracheitis are rarely due to streptococci. The syndrome of sudden onset of fever, sore throat, "beefy" redness of the pharynx and pharyngeal exudate suggests the diagnosis. Cervical lymphadenitis and the presence of leukocytosis add further evidence for it.

Penicillin appears to be the drug of choice for prophylaxis or therapy. Various routes of administration are discussed by the author. For continuous chemoprophylaxis 200,000 to 250,000 units of oral penicillin daily, 1,200,000 units of benzathine penicillin intramuscularly once monthly or 1 Gm. of sulfadiazine daily is recommended.

HARRIS

Catanzaro, F. J., Stetson, C. A., Morris, A., Chamovitz, R., Rammelkamp, C. H., Stolzer, B. L. and Perry, W. D.: The Role of the Streptococcus in the Pathogenesis of Rheumatic Fever. Am. J. Med. **17:** 749 (Dec.), 1954.

Treatment of streptococcal infections with penicillin nine days after the onset of illness eliminated the infecting organism from the throat, failed to inhibit antibody formation appreciably, and significantly reduced the attack rate of rheumatic fever. In contrast, the administration of sulfadiazine during the acute streptococcal illness suppressed antibody formation somewhat more effectively than penicillin at 21 days but did not eradicate the organism nor prevent rheumatic fever. The patients who received no specific therapy sustained maximum antibody formation, remained carriers and experienced the usual attack of rheumatic fever.

The data strongly suggest that the development of rheumatic fever requires the presence of living streptococci throughout convalescence. This conclusion is in conflict with certain hypotheses pre-

viously advanced to explain the pathogenesis of rheumatic fever but may be in accord with the concept that hypersensitivity of the tuberculin or "delayed" type is involved. This type of hypersensitivity is obviously unrelated to the presence or titer of circulating antibody but appears to depend upon the gradual liberation of small quantities of the antigen involved.

HARRIS

Likoff, W., Berkowitz, D., Geyer, S., Strauss, H. and Reale, A.: The Value of Blood Volume Determinations in the Study of Patients Undergoing Surgery for Rheumatic Heart Disease. Am. Heart J. **49:** 1 (Jan.), 1955.

The total blood volume was determined by using the radioactive iodinated (I^{131}) human serum albumin method in 55 normal subjects and one hundred patients with rheumatic heart disease. The patients with rheumatic heart disease included those in and not in congestive heart failure. The average total blood volume in 45 normal individuals was 75.1 c.c. per Kg. The average total blood volume in 54 patients with compensated rheumatic heart disease was within normal limits. The average total blood volume in 20 patients with congestive failure was elevated above that of the normals and fell progressively as compensation was restored in nine of eleven subjects studied serially. Of 59 patients with a normal total blood volume undergoing surgery, two died and one developed congestive heart failure for a combined morbidity-mortality of 5.6 per cent. Four of the 26 patients with an elevated blood volume died following surgery, and eleven developed decompensation for a combined morbidity-mortality of 57.7 per cent. This morbidity and mortality of patients with elevated total blood volumes who were operated upon for acquired heart disease were sharply increased beyond normal expectations, regardless of the clinical picture.

RINZLER

Pampush, J. J. and Bruce, R. A.: Natural History, Functional Capacity and Exercise Tolerance of Unoperated Patients with Mitral Stenosis. Am. J. M. Sc. **228:** 605 (Dec.), 1954.

Fifteen unoperated patients with mitral stenosis were evaluated thoroughly by conventional methods including a standardized exercise tolerance test. Approximately one year later, a reevaluation was made on the 12 surviving patients. Three class IV patients died of congestive failure during the interval. The impressive clinical changes in the patients, examined after one year, were the reduction in the incidence of symptoms, signs and treatment of pulmonary congestion and cardiac edema. There was no substantial change in the clinical classification of their functional capacities. Presumably, the improved status represented recovery from the precipitating factors responsible for the manifestations of cardiac insufficiency that prompted the patients to seek medical consultations. The exercise tolerance tests revealed improvement of only borderline significance with respect to physical fitness indices, endurance and respiratory efficiency. These changes reflect the improved pulmonary function associated with a decrease in pulmonary congestion. The authors conclude that the patients should not be submitted to surgery unless there is persistent disability secondary to pulmonary engorgement, despite prolonged medical treatment. The exercise tolerance test supplements the clinical appraisal and may be useful in determining the optimal time for surgical intervention. It is emphasized that measurements of functional capacity should be made post-operatively to determine whether a significant change occurs within a year or so after commissurotomy.

SHUMAN

Bergeron, J., Abelmann, W. H., Vazquez-Milan, H. and Ellis, L. B.: Aortic Stenosis—Clinical Manifestations and Course of the Disease. Arch. Int. Med. **94:** 911 (Dec.), 1954.

Clinical and autopsy records of 100 cases of aortic stenosis without significant involvement of other valves are reviewed and the clinical symptoms and signs and the course of the disease examined in relation to the severity of the lesion. Aortic stenosis was marked in 49, moderate in 32 and mild in 19 cases. The mean age for the group was 69 years. Men outnumbered women three to one. Symptoms in general were those of heart failure. One-third of the patients complained of pain referable to the heart; in only half of these was the pain diagnostic of angina pectoris. Typical angina was more often accompanied by coronary atherosclerosis than was atypical cardiac pain. Dizziness was a symptom in one-quarter of the group, and syncope was reported in one-eighth. Even in the presence of severe aortic stenosis, systolic basal thrill and murmur were often absent, the second aortic sound frequently was judged normal, and the diastolic pressure not infrequently was low and was associated with a wide pulse pressure. A harsh systolic murmur, loudest at the apex or heard exclusively at the apex, at times was the only physical sign of aortic stenosis. Systolic and/or diastolic hypertension was present in one-third of the patients. Electrocardiographic evidence of left ventricular hypertrophy was seen in only 38 per cent of the tracings reviewed, while auricular fibrillation was present in 30 per cent.

The nature of symptoms and their severity appeared of little aid in assessing the degree of stenosis, perhaps because of the degree of associated coronary atherosclerosis, myocardial fibrosis and aortic regurgitation. A rapid evolution of symptoms favored a high degree of stenosis. An absent second aortic sound, an aortic systolic murmur grade IV or louder in intensity, or an aortic systolic thrill favored marked stenosis. Blood pressure and pulse pressure

were of limited value in assessing the degree of stenosis, but a narrow pulse pressure indicated moderate to marked stenosis. While the asymptomatic phase of the disease was often long and permitted the attainment of advanced age, once cardiac symptoms had appeared, the prognosis became guarded. The appearance of congestive failure was a grave sign, as was atrial fibrillation. When either of these was accompanied by cardiac pain or syncope, death followed within weeks to months.

BERNSTEIN

ROENTGENOLOGY

Batt, H. D., Allen, J. M., Treder, F. H. and Shapiro, R.: Photofluorographic Detection of Cardiovascular Disease in a General Hospital. New England J. Med. **251:** 934, (Dec. 2), 1954.

A series of 6439 adult patients were studied by means of routine photofluorograms upon admission to the Hospital of St. Raphael during 1953. On the basis of this admission photofluorogram 709 patients were suspected of having a cardiovascular abnormality. The followup study of 595 of these patients revealed cardiovascular disease in 497 of them (83 per cent). One hundred and ninety-six (47 per cent) were unaware of the cardiovascular disorder. The study was limited to ambulatory patients. The study included a left lateral view in addition to the routine posteroanterior film, except in patients who were very obese and in the prenatal group. The lateral view was of value in appraising the influence of body build, scoliosis and pectus excavatum upon the cardiac configuration observed in the posteroanterior projection. Although the lateral view did not increase the absolute yield of abnormal cases, it did help to increase the accuracy of the reading.

ROSENBAUM

SURGERY IN HEART AND VASCULAR SYSTEM

DeBakey, M. E., Cooley, D. A. and Creech, O. Jr.: Treatment of Aneurysms and Occlusive Disease of the Aorta by Resection. J.A.M.A. **157:** 203 (Jan. 15), 1955.

Aneurysms and occlusive lesions, the most common forms of aortic disease, are associated with progressively disabling manifestations and a grave prognosis. Therapy of these conditions consists of extirpation of the lesion and restoration of function by the use of aortic homografts or orlon cloth prosthesis. The success of this form of therapy is dependent upon a number of factors, such as the nature, extent and location of the lesion. In occlusive disease with well developed collateral circulation and localization, there are few or no limitations to the safe performance of the procedure. In aneurysms, however, the type and location of the lesion is very important in determining the feasibility of the procedure. In sacciform lesions tangential excision and lateral aortography may be readily done anywhere on the aorta. Fusiform aneurysms, requiring resection of the involved segment of the aorta, impose the necessity for temporary arrest of aortic circulation. Aneurysms, arising below the origin of the renal arteries, pose less of a problem than aneurysms of the thoracic aorta. Hypothermia may help in averting ischemic effects following temporary arrest of aortic circulation. There are two types of occlusive disease of the abdominal aorta; those with complete and those with incomplete block. Resection with homograft replacement is the treatment of choice where the occlusive process is localized to the terminal aorta and bifurcation but in cases associated with extensive and diffuse peripheral arteriosclerosis obliterans the procedure is contraindicated. Of the 150 patients undergoing aortic resection, 89 were operated on for aneurysm; in 13 the thoracic aorta was involved; in 76, the abdominal aorta. The remaining 61 patients were operated for occlusive disease, 10 for coarctation and 51 for thromboobliterative disease of the abdominal aorta. In the group with aneurysm there were 20 deaths, or an operative mortality of 22 per cent. In the group with occlusive lesions there were two deaths and a mortality of 3 per cent. Orlon cloth prostheses have been used to replace the aortic bifurcation in 13 patients, with satisfactory results. With few exceptions, the surviving patients in this series have been completely relieved of their symptoms. The gratifying results obtained so far suggest that resection is the most effective means of dealing with aneurysms and occlusive disease of the aorta.

KITCHELL

Luke, J. C.: Management of Segmental Occlusion of Major Arteries. Geriatrics **10:** 5 (Jan.), 1955.

The paper is concerned with those patients in whom clinical evidence and arteriographic proof indicates segmental occlusion of one of the major arteries leading to the lower extremity. The methods of clinical detection are discussed. Data, concerning 22 patients surgically treated for segmental occlusion of a major artery leading to the leg, are presented. Eight cases with aortic and iliac blockage were treated by thromboendarterectomy, two by excision and replacement by stored hemografts. Twelve cases had resection of occluded areas of the superficial femoral artery with replacement by autogenous saphenous vein grafts.

RINZLER

Crafoord, C. and Werko, L.: Surgical Treatment of Rheumatic Heart Disease. Am. J. Med. **17:** 811 (Dec.), 1954.

The authors review the pathophysiology of rheumatic heart disease and discuss the indications and surgical treatment of rheumatic valvular heart disease. Of all the methods, suggested and in some cases attempted, only the valvulotomies for mitral

stenosis and pulmonary stenosis have given results that have established them as suitable in the surgical treatment of the various valvular lesions caused by rheumatic fever, other infectious diseases or of congenital origin. They are also the only operations that do not carry an undue mortality rate and are technically easy enough to be recommended for general use. With the use of extra-corporeal oxygenation and circulation, perhaps combined with hypothermia, heart surgery will enter a new era and operative methods now impossible to conceive will add to the possibilities of treatment in patients with rheumatic heart disease.

HARRIS

Beck, C. S.: The Technique of Opening the Stenotic Mitral Valve. J.A.M.A. **156:** 1400 (Dec. 11), 1954.

The author discusses the method of dilating or tearing the commissures by passing the first joint of the finger through the valvular orifice. After this is performed with the gloved finger, umbilical tape is wrapped around the first joint of the finger and a second glove is applied and the valve is further dilated. This is repeated in stages until the valve is enlarged to the desired degree. In 15 months this method was used on about 200 patients and has almost eliminated the creation of mitral valve regurgitation as a complication of valvotomy.

KITCHELL

VASCULAR DISEASE

Szilagyi, D. E. and Overhulse, P. R.: Segmental Aorto-iliac and Femoral Arterial Occlusion. J.A.M.A. **157:** 426 (Jan. 29), 1955.

In the past few years an increasing number of cases of peripheral arterial deficiency, having involvement of relatively short segments of the large arteries supplying the lower limbs, have been recognized. Although pathologic distinction from ordinary arteriosclerosis is not clear, these variants of occlusive arterial disease are amenable to direct surgical methods of treatment. Twenty-seven such cases were observed by the authors. They point out, that although angiography is important, there are distinguishing clinical features that often make possible a differential diagnosis on clinical grounds alone. Followup observations extending from 3 weeks to 11 months in 14 cases of segmental arterial occlusion involving 19 operative procedures yielded good results in 76 per cent of the instances. In those cases not benefited by the treatment the condition of the affected limb was not made worse by operation. It, therefore, appears that resection with arterial homograft replacement is a promising method of treatment. In two such operations involving cases of diffuse arteriosclerosis with incidental segmental occlusion and impending gangrene, one ended in failure. However, theoretic considerations would suggest that in selected cases of peripheral arterial disease due to diffuse arteriosclerosis resection and arterial grafting may offer some help.

KITCHELL

Opdyke, D. F., Rosenberg, A., Silver, R., Ott, W. H. and Siegel, H.: Effect of Chronic Injection of a Heparin Complex on Aortic Atherosclerosis in Cholesterol-fed Chickens. J. Lab. & Clin. Med. **45:** 270 (Feb.), 1955.

Four groups of 8 week-old white Leghorn cockerels were placed on a high cholesterol diet, two of the groups receiving a daily injection of 8 mg. of a butacaine-heparin complex (equivalent to 3 mg. heparin) intramuscularly for 8 weeks, the other two groups serving as controls. There was no statistically significant inhibitory action of heparin on the incidence and severity of thoracic aorta atherosclerosis. However, there was a decrease in total plasma cholesterol and other lipid fractions after four weeks of heparin injection. Chronic heparin injection also tended to prevent the rise of S_f 10–20 class molecules which was observed in the cholesterol-fed chickens.

The possibility is discussed that the failure to obtain clear-cut results may be due to the difficulty in maintaining an adequate blood level of heparin, despite the use of a slowly absorbed heparin complex such as the butacaine-heparin preparation.

CORTELL

Hellman, L., Rosenfeld, R. S., Eidinoff, M. L., Fukushima, D. K., Gallagher, T. F., Wang, C-I. and Adlersberg, D.: Isotopic Studies of Plasma Cholesterol of Endogenous and Exogenous Origins. J. Clin. Invest. **34:** 48 (Jan.), 1955.

Cholesterol labelled with either isotopic carbon or hydrogen was administered orally to human subjects and the incorporation into plasma cholesterol was observed. By use of labeled acetate and cholesterol it was possible to study both exogenous and endogenous cholesterol metabolism.

Traces of orally labeled cholesterol were detected in the plasma within one hour, but maximum radioactivity was not attained until two or three days. On the other hand, the peak of specific activity of plasma cholesterol formed in vivo from labeled acetate was eight hours.

Aside from the early differences in the appearance times, the data suggest that cholesterol derived from the diet is eventually indistinguishably mixed with cholesterol synthesized in the body.

WAIFE

Wawzonek, S., Ponseti, I. V., Shepard, R. S. and Wiedenmann, L. G.: Epiphyseal Plate Lesions, Degenerative Arthritis, and Dissecting Aneurysm of the Aorta Produced by Aminonitriles. Science **121:** 63 (Jan. 14), 1955.

Beta-Aminopropionitrile produced lesions of the epiphyseal plates, degenerative arthritis and dissecting thoracic aortic aneurysm, when fed to weanl-

ing rats in concentration of 0.1 to 1.0 per cent. These lesions appear to be histologically identical with those of lathyrism (diets of sweet pea seeds). The aneurysm was fatal in one rat after 32 days of feeding at the 0.4 per cent level.

WAIFE

Marigold, Q. and Roth, F.: The Aortic Arch Syndrome (Maladie sans pouls). Schweiz. med. Wchnschr. **84:** 1192 (Oct.), 1954.

A case of aortic arch syndrome (pulseless disease) in a 46 year old woman caused by progressive obliterative vascular disease of unknown etiology is described. Over a period of 15 years the process had led to total occlusion of both subclavian, the left common carotid, and the right vertebral arteries, with nearly complete loss of pulses in the arms and neck, right sided hemiplegia and loss of vision in the left eye. In view of the advancing impairment of cerebral circulation, bilateral stellectomy and resection of the thrombosed left common carotid artery were performed. The resected portion showed the histologic pattern of endangiitis obliterans. The symptomatology and possible etiology of the syndrome are discussed and attention is drawn to a clinical entity described previously under the term "arteriitis in young females."

PICK

Swank, R. L.: Effect of High Fat Feedings on Viscosity of the Blood. Science **120:** 427 (Sept. 10), 1954.

Blood viscosity was measured as the time required for 0.1 ml. of blood to flow through a 25 gauge needle inserted in a vein under standardized conditions.

Hamsters on a high fat diet were given a single fat meal of 2 to 3 ml. of 35 per cent cream and the blood viscosity determined at frequent intervals afterwards. The increase in viscosity which was first noted about 3 hours after the cream feeding reached its peak in 6 to 9 hours. By the end of 24 hours, the viscosity returned to normal, but there was a significant drop in hematocrit. This is thought to be due to "sticking" of erythrocytes. The increase in viscosity was associated with hyperemia, cyanosis, and a reduced bleeding tendency.

Heparin injections produced a transient reduction of the excess viscosity.

WAIFE

Walker, A. R. P., and Arvidsson, U. B.: Fat Intake, Serum Cholesterol Concentration, and Atherosclerosis in the South African Bantu. Part I. Low Fat Intake and the Age Trend of Serum Cholesterol Concentration in the South African Bantu. J. Clin. Invest. **33:** 1358 (Oct.), 1954.

The South African Bantu habitually eats a diet containing about half as much fat as the American diet. This study reports a survey of blood cholesterol levels among 218 Bantu subjects of all ages.

Up to age 40 there was no significant difference between mean values for the Bantus and those reported by Keys from Minnesota. After this age, however, the serum cholesterol levels are significantly lower among the Bantus.

The urban native, consuming a European diet (higher in fat), had a significantly higher mean cholesterol level than the rural Bantu. Other factors, such as caloric intake, liver disease, and racial stock, seem to have little importance in influencing serum cholesterol levels. Probably the low fat diet was the most significant factor, although the high fibre content of the diet may also bear some responsibility.

WAIFE

Edwards, W. S. and Lyons, C.: Traumatic Arterial Spasm and Thrombosis. Ann. Surg. **140:** 318 (Sept.), 1954.

The authors presented several illustrative cases of arterial spasm and thrombosis following local trauma to a limb and drew certain conclusions from them regarding the proper therapeutic approach. They pointed out that one could not depend upon sympathetic interruption alone, since traumatic spasm of large arteries is not always due to overactivity of the sympathetic nervous system. Fasciotomy is of definite value in arterial lacerations if there is a tense subfascial hematoma constricting the collateral blood supply. Furthermore, in cases of complete arterial obstruction as a result of spasm or thrombosis, a similar firm swelling may occur due to intense edema of ischemic muscle, and under these circumstances the constricting envelope can also be released by fasciotomy. If exploration reveals a segment of artery in spasm, topical papaverine may prove efficacious in removing this state. If spasm persists and if the length of involved vessel is not too great, it is probably advisable to resect this portion and reestablish continuity with a venous or arterial graft or by reanastomosing the cut ends.

ABRAMSON

Gottfried, S. P., Pope, R. H., Friedman, N. H., Akerson, I. B. and DiMauro, S.: Lipoprotein Studies in Atherosclerotic and Lipemic Individuals by Means of Paper Electrophoresis. Am. J. M. Sc. **229:** 34 (Jan.), 1955.

Total serum lipids, total cholesterol, alpha and beta lipoprotein determinations were performed on eight patients with arteriosclerotic disease, 39 control subjects and 17 subjects with lipeia; both sexes were represented with an age range of 20 to 55 years. Among the normals, the beta lipoproteins were found to be higher in men in their twenties than in women of the same age. No variations were observed in the alpha lipoprotein, greater than that seen in the controls. These values gradually decreased with the passage of time. There appears to be no apparent relationship between lipids, cholesterol and the

lipoproteins. Of the eight atherosclerotic patients, all showed at least one elevated serum lipid or total cholesterol or both. In the lipemic group an elevated beta lipoprotein was obtained in about 50 per cent of those studied.

SHUMAN

Bigelow, N. H.: Multiple Intracranial Arterial Aneurysms. Arch. Neurol. & Psychiat. **73:** 76 (Jan.), 1955.

Little more than casual notice has been given to the presence of multiple intracranial arterial aneurysms. Therefore, an analysis of this problem in terms of its significance seemed indicated.

A review of the literature shows that the incidence of multiple intracranial aneurysms was slightly over 10 per cent. One impression gained from this review indicates that multiple aneurysms occurred more frequently than they were found or reported as their fiscovery required diligent search. Data collected drom the Albany Hospital autopsy files showed nearly 25 per cent of intracranial aneurysm cases to be multiple. Only 5 per cent of these were found at operation. Occasional mention has been made of bilateral or symmetrical aneurysm, and the literature is reviewed in detail on this point.

With the advent of angiography, x-ray film demonstration of multiple aneurysms has frequently been made and the desirability of bilateral carotid angiography has been advocated. Rarely do two of the aneurysms rupture simultaneously. However, reports do mention the leakage of a second aneurysm at some subsequent period. The possibility that a second aneurysm might become symptomatic should be kept in mind. Intracranial aneurysms do not seem to be associated with extracranial aneurysms or other types of intracranial vascular lesions.

Anomalies of the circle of Willis, coarctation of the aorta and congenital polycystic renal disease have been found in association with berry type intracranial aneurysms often enough to be noteworthy. Since all of these lesions represent developmental defects, their coexistence may be more than coincidental and, therefore, merits attention. It is possible that the altered hemodynamics resulting from the vascular anomalies may favor the development of aneurysms. Arteriosclerosis, congenital defects, and elevation of intravascular pressure are possible causes. Multiple miliary aneurysms have been found. Mycotic intracranial aneurysms are not often multiple. They are usually caused by septic emboli and occur in small arterial twigs. Syphilitic intracranial aneurysms are rare.

WECHSLER

Blainey, J. D., Hardwicke, J. and Whitfield, A. G. W.: The Nephrotic Syndrome Associated with Thrombosis of the Renal Veins. Lancet **2:** 1208, (Dec. 11), 1954.

Two cases of renal vein thrombosis and one of constrictive pericarditis with the nephrotic syndrome are described. In the last patient, a 50 year-old woman with otherwise typical constrictive pericarditis, there was also proteinuria of 13 to 17 Gm. per day, serum albumin of 1.6 Gm. per cent, serum cholesterol of 702 mg. per cent. After cardiac decortication, the serum albumin rose to 5.0 Gm. per cent, serum cholesterol fell to 245 mg. per cent and the proteinuria disappeared.

MCKUSICK

Jacobson, S. A.: Analysis of Some Factors in Spontaneous Subarachnoid Hemorrhage. Arch. Neurol. and Psychiat. **72:** 712 (Dec.), 1954.

The mortality of subarachnoid hemorrhage falls into two categories: those cases in which death is due to the first attack, and those in which the patient succumbs to a subsequent bleeding. A great deal of attention has been given to the latter since many of these people can be helped with definitive treatment. The physician is able to offer only palliative and supportive treatment to those who die in the first attack, which group represents approximately 28 per cent of all cases with subarachnoid hemorrhage. Only four of the signs found in this condition are reported in the literature in sufficient detail to be analyzed for their prognostic significance. These signs are coma, convulsions, hypertension, and papilledema. The appearance of any of the first three signs, singly, is indicative of a poor prognosis for life. Age has no effect on the mortality rate. Approximately 10 per cent of all patients with subarachnoid hemorrhage are maimed to a significant degree. Aneurysm with subarachnoid hemorrhage occurs in the neighborhood of 50 per cent of cases. A frequent contraindication to surgery is multiplicity of the aneurysm, which is present in about 13 per cent of all patients that have aneurysms. This finding shows that a thorough angiographic study is indicated before surgical treatment is done.

BERNSTEIN

Mandel, W., Evans, E. W. and Walford, R. L.: Dissecting Aortic Aneurysm During Pregnancy. New England J. Med. **251:** 1059 (Dec. 23), 1954.

The authors describe a woman aged 20 years who died of a dissecting aortic aneurysm during the fifth week of her first pregnancy. The patient had been hypertensive prior to the pregnancy. This is said to be the thirty-seventh reported case of dissecting aneurysm during pregnancy. Approximately one-half of the cases of dissecting aneurysm of the aorta which have been recorded in women under the age of 40, were pregnant at the time. In the reported case there was considerably medionecrosis of the aorta, proliferation of the vaso vasorum with early rhexis and hemorrhage into degenerated media and sclerosis of advential vasa in the ascending aorta.

ROSENBAUM

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

MODIFIED RHEUMATIC FEVER DIAGNOSTIC CRITERIA

Reprints of *Jones Criteria (Modified) for Guidance in the Diagnosis of Rheumatic Fever* are being made available to the medical profession. The revised criteria were published in the September, 1955 issue of the Association's monthly bulletin for physicians, *Modern Concepts of Cardiovascular Disease.*

The modified criteria are based on the diagnostic standards first published by the late T. Duckett Jones, M.D. in 1944, and generally accepted throughout the United States and in many other nations.

Avoiding Overdiagnosis

In an introductory report, the Committee on Standards and Criteria for Programs of Care of the Association's Council on Rheumatic Fever and Congenital Heart Disease emphasizes that because "the tragedy which may lie in the wake of the false diagnosis of rheumatic fever may be even greater than the possible harm of missed recognition," the "criteria are necessary to minimize both overdiagnosis and underdiagnosis." The committee also places stress on the fact that the criteria are not designed to "substitute for the wisdom and judgement of the clinician."

Division of Criteria

The diagnostic guide lists and describes five "major" criteria and six "minor" criteria. The division into 'major' and 'minor' categories is based upon the relative occurrence of these factors in rheumatic fever and in other disease syndromes. "These major and minor categories have no significance beyond their diagnostic import either as to prognosis, amount of 'rheumatic activity,' or severity of acute illness," the statement points out.

Requests for reprints of the full diagnostic guide should be addressed to the Association, 44 East 23 Street, New York 10, N. Y.

ESTABLISH FUND IN MEMORY OF T. DUCKETT JONES

Establishment of a T. Duckett Jones Memorial Fund devoted to research has been announced by a group of former friends and associates of the outstanding rheumatic fever research investigator and clinician who died last November. At the time of his death, Dr. Jones was Vice President and Medical Director of the Helen Hay Whitney Foundation of New York. He had served for several years as Vice President of the American Heart Association and was one of the leading figures in the Association's Council on Rheumatic Fever and Congenital Heart Disease. A posthumous Gold Heart award was bestowed on Dr. Jones at the Association's Annual Meeting last month.

Rheumatic fever research, the subject of so much of Dr. Jones' devoted effort, is to be given priority although not exclusive claim to the fund's resources. Among the projects already suggested are fellowships for promising young investigators, short-term support for investigators holding permanent positions to permit completion of studies or projects and the establishment of a T. Duckett Jones professorship. The committee would welcome additional suggestions.

Tax exempt contributions may be sent to the T. Duckett Jones Memorial Fund, 525 East 68 Street, New York 21, N. Y.

LASKER AND BLAKESLEE AWARDS PRESENTED

The 1955 Albert Lasker Award and Howard W. Blakeslee Awards of the Association were scheduled for presentation at the Annual Meeting and Scientific Sessions in New Orleans in October.

The Lasker Award for distinguished achievement in the field of cardiovascular diseases was presented to Carl J. Wiggers, M.D., Professor Emeritus and former Director of the Department of Physiology at the School of Medicine

of Western Reserve University, now Honorary Professor of Physiology at the Frank E. Bunts Educational Institute, Cleveland, and Editor of *Circulation Research*, the Association's journal of fundamental studies. The "dean of cardiovascular physiologists" and former President of the American Physiological Society was previously honored by the Association's Gold Heart Award in 1952 and by the dedication of a special issue of *Circulation* in 1951. The Lasker Award consists of a statuette of the Winged Victory of Samothrace and $1,000.

The Blakeslee Awards are made annually for outstanding reporting in the cardiovascular field. Four awards of $500 each were made this year to the following:

Mrs. Frances Burns, medical writer of the Boston Daily Globe, for a series of 13 articles on advances in cardiovascular research, treatment and prevention.

Miss Jane Stafford, medical writer of Washington, D. C., for year-round coverage of important cardiovascular developments syndicated to newspapers and magazines by Science Service.

William Peters, Pelham Manor, N. Y., for his article, "A New Heart for Pamela," published in the September, 1954, issue of Cosmopolitan Magazine. The article describes an operation employing the cross-circulation technique developed by C. Walton Lillehei, M.D., and his associates at the University of Minnesota.

The Columbia Broadcasting System for the film "Gate 27," telecast as part of the series known as *The Search*. The film describes research at the Laboratory of Physiological Hygiene of the University of Minnesota on the relationship of diet, vocation and other factors to cardiovascular disease.

DR. SCHUYLER JOINS ASSOCIATION AS ASSISTANT MEDICAL DIRECTOR

Leonard H. Schuyler, M.D., New York has been appointed as an Assistant Medical Director of the Association. He will aid in the administration of the research support and professional education programs.

Dr. Schuyler, a graduate of the Duke University Medical School, formerly was a research fellow in medicine at the Vascular Research Laboratory of the New York Hospital-Cornell University Medical School.

Miss Winifred Devlin, R.N., has been appointed as Consultant Nurse in Cardiovascular Diseases for the newly-established Cardiovascular Nursing Advisory Service, a joint project of the Association and the National League for Nursing.

Miss Devlin, former Industrial Nurse Consultant in the U. S. Public Health Service, will assist Heart Associations throughout the country in establishing closer relations with the nursing profession and in providing special educational services for nurses.

R. H. HALSEY, M.D.

Robert H. Halsey, M.D., one of the leading figures in the organization of both the American and New York Heart Associations, died on September 15 while visiting in the Province of Quebec. Dr. Halsey was 82 years old.

The New York Cardiologist presided at the founding meeting of the American Heart Association which was held in St. Louis in 1922. Previously he had played an active role in the organization of the Association for the Prevention and Relief of Heart Disease, which later became the New York Heart Association. Dr. Halsey was the first secretary of the National Association, and in 1931–32, he served as its president.

Dr. Halsey's unique contributions to the recognition of the importance of cardiovascular diseases as the leading cause of deaths in the U. S. and to the establishment and growth of the Heart organization were recognized in 1950 when he received the American Heart Association's Gold Heart Award.

Dr. Halsey had served for many years as Professor of Medicine at New York Postgraduate Medical School and Hospital and Consultant at the University Hospital of the New York University-Bellevue Medical Center.

ADVANCE CARDIOGRAPHY COURSE SCHEDULED AT MICHAEL REESE

An advanced course in *Interpretation of Complex Arrhythmias* will be given at the Michael Reese Hospital in Chicago for experienced

electrocardiographers. The course will consist of daily 9:00 AM to 5:00 PM classes from December 5–9. The classes will be conducted by Louis N. Katz, M.D., Richard Langendorf, M.D. and Alfred Pick, M.D.

Further information and a copy of the lecture schedule may be obtained from the Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

TULANE OFFERS PROGRAM ON ELECTROLYTE BALANCE

The Division of Graduate Medicine at the Tulane University School of Medicine, New Orleans, will present a five-day program on *Fluid and Electrolyte Balance*, January 16–21, 1956. The course, under the chairmanship of George E. Burch, M.D., Professor of Internal Medicine, will emphasize clinical applications of the fundamental principles of water and electrolyte metabolism.

Inquiries may be addressed to the Director, Division of Graduate Medicine, 1430 Tulane Avenue, New Orleans 12, La.

1958 WORLD CARDIOLOGY CONGRESS TO HEAR EPIDEMIOLOGIC REPORTS

Epidemiologic reports from all nations will be a feature of the Third World Congress of Cardiology when it is held in Brussels, Belgium, September 14–21, 1958. The International Society of Cardiology has requested each affiliated cardiologic organization, including the American Heart Association, to prepare a report on the main epidemiologic problems in their respective countries.

The International Society has also urged the affiliated groups to submit additional suggestions for specific topics of discussion at the Brussels Congress.

DEVELOP CARDIAC EMERGENCY KIT

A newly developed portable cardiac emergency kit for physicians and hospitals is being distributed by the Essex County (New Jersey) Heart Association.

The sturdy wood and leather kit includes a brief diagnostic and therapeutic guide for 13 frequently occurring cardiac emergencies and was prepared by Jacob J. Silverman, M.D., Staten Island, N. Y., Arthur Bernstein, M.D., Newark, N. J. and Harold B. Trachtenberg, M.D., New York, N. Y. It also provides clamps and spaces for 34 most commonly needed drugs and equipment for their use.

The kit weighs about eight pounds empty and is 16 inches long, 12 inches deep and six inches wide. Kits may be obtained at a cost of $15 plus shipping charges each from the Essex County Heart Association, 120 Evergreen Place, East Orange, N. J.

INTER-AMERICAN CARDIOLOGY SOCIETY ANNOUNCEMENTS

The Fifth Inter-American Congress of Cardiology will be held in Havana, Cuba, in November, 1956.

The Colombian Society of Cardiology is organizing its first national cardiology congress to be held in July, 1956. Tentative plans call for placing emphasis on peripheral vascular problems and hypertension. Information may be obtained from the Sociedad Colombiana de Cardiologia, Carrera 13 No. 48-26, Bogota, Colombia, S. A.

MEETING CALENDAR

Nov. 3: Midwestern Section, American Federation for Clinical Research, Northwestern University Medical Campus, Chicago. Robert J. Glaser, M.D., Barnes Hospital, 600 South Kingshighway, St. Louis 10.

Nov. 6–7: American Society for the Study of Arteriosclerosis, Hotel Sheraton, Chicago. Dr. O. J. Pollak, P.O. Box 228, Dover, Del.

Nov. 14–17: Congress of International Society for Research on Anesthesia, Boca Raton, Fla. R. J. Whitacre, M.D., 13951 Terrace Road Cleveland 12.

Nov. 14–18: Annual Meeting, American Public Health Association, Kansas City, Mo. R. M. Atwater, 1790 Broadway, New York 19.

Nov. 11–12: Society of Clinical Surgery, New Orleans. Dr. Frank F. Albritten, Jr., University of Kansas Medical Center, Kansas City, Kan.

Nov. 14–18: American School Health Association, Kansas City, Mo. A. O. DeWeese, 515 E. Main St., Kent, O.

Dec. 2: Eastern Section, American Federation for Clinical Research, College of Physicians Bldg., Philadelphia. Charles R. Shuman, M.D., Temple University Hospital, Broad and Ontario Streets, Philadelphia 40.

Dec. 11–16: Radiological Society of North America, Chicago. D. S. Childs, 713 E. Genesee St., Syracuse, N. Y.

Dec. 13: American Academy of Obstetrics and Gyne-

cology, Chicago. C. Paul Hodgkinson, 116 S. Michigan Blvd., Chicago 3.

Jan. 20: Southern Section, American Federation for Clinical Research, New Orleans. John H. Moyer, M.D., Baylor University College of Medicine, 1200 M. D. Anderson Blvd., Houston.

Jan. 25: Western Section, American Federation for Clinical Research, Carmel, Calif. B. H. Scribner, M.D., Veterans Administration Hospital, Seattle 8, Wash.

Feb. 6–8: American Academy of Allergy, St. Louis, Francis C. Lowell, 65 E. Newton St., Boston.

Feb. 10–11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6.

March 24–25: American Psychosomatic Society, Sheraton Plaza Hotel, Boston. Abstracts must be submitted by Dec. 1 to Stanley Cobb, M.D., 551 Madison Avenue, New York 22.

ABROAD

Nov. 18–26: Venezuelan Congress of Medical Sciences, Caracas. Dr. A. L. Briceno Rossi, Sec.-Gen. Comision Organizadora del VI Congreso Venezolano de Ciencias Medicas, Apartado 4112, Ofic. del Este, Caracas, Venezuela.

Nov. 19–24: Congress of International College of Surgeons, Buenos Aires. Max Thorek, M.D., 1516 Lake Shore Drive, Chicago.

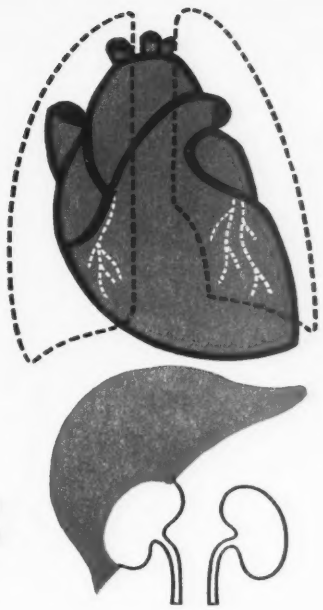
Nov. 21: Symposium of the French Association of Medical Biology, Paris. Dr. D. Durupt, 20 rue de la Pompe, Paris 16.

Nov. 23–25: First International Congress on Documentation of Applied Chemistry, London. Hon. Secretary of the Congress, 56 Victoria Street, London S.W. 1.

Jan. 20–27: Pan-American Congress of Gastro-Enterology, Havana. Dr. Norberto E. Stapler, 1267 J.E. Uriburu, Buenos Aires.

h

know your diuretic



how safe is the diuretic you prescribe?

the utmost in safety, confirmed by long clinical usage, is one reason more physicians choose the organomercurials for diuresis. Their dependable action does not involve production of acidosis or specific depletion of potassium, and side effects due to widespread enzyme inhibition are absent.

TABLET
NEOHYDRIN®
BRAND OF CHLORMERODRIN (18.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA IN EACH TABLET)

no "rest" periods • no refractoriness

NEOHYDRIN can be prescribed every day, seven days a week as needed

a standard for initial control of severe failure

MERCUHYDRIN® SODIUM
BRAND OF MERALLURIDE INJECTION

Leadership in diuretic research
Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

88555

Circulation

NOVEMBER 1955
VOL. XII NO. 5

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS